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No. 2025-1281(L); 2025-1282

**In the United States Court of Appeals
for the Federal Circuit**



MELINTA THERAPEUTICS, LLC, MELINTA SUBSIDIARY CORP.,
REMPEX PHARMACEUTICALS, INC.,

Plaintiffs-Appellees,

-v-

NEXUS PHARMACEUTICALS, INC.,

Defendant-Appellant.

On Appeal from the U.S. District Court for the Northern District of Illinois,
Nos. 1:21-cv-02636, 1:21-cv-05995 (Hon. John F. Kness, Judge)

Joint Appendix

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**IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION**

MELINTA THERAPEUTICS, LLC,
MELINTA SUBSIDIARY CORP, and
REMPEX PHARMACEUTICALS, INC.,

Plaintiffs,

v.

NEXUS PHARMACEUTICALS, INC.,

Defendant.

No. 21-cv-02636

Judge John F. Kness

FINDINGS OF FACT AND CONCLUSIONS OF LAW

This matter is before the Court for decision on the infringement and validity of Claims 1, 7, and 18 of the U.S. Patent No. 9,084,802 (the “’802 Patent”) and Claim 27 of the U.S. Patent No. 9,278,105 (the “’105 Patent”) (together, the “patents-in-suit”). The patents-in-suit cover the intravenous administration of Minocin® (minocycline) for injection (“Minocin”) product, an aqueous solution consisting of minocycline and magnesium that is used to treat bacterial infections. The matter was before the Court for a bench trial over four days from June 6, 2023 to June 9, 2023. Closing arguments were heard separately on August 15, 2023. This is a Hatch-Waxman patent infringement action brought by Melinta Therapeutics, LLC; Melinta Subsidiary Corp.; and Rempex Pharmaceuticals, Inc. (together, the “Plaintiffs”) against Nexus Pharmaceuticals, Inc. (the “Defendant”). It arises out of Defendant’s filing of Abbreviated New Drug Application (“ANDA”) No. 214934 containing a

Paragraph IV certification with the Food and Drug Administration (“FDA”) seeking approval to market a generic version of Minocin identified in the ANDA.

Having considered the evidence presented during the bench trial, the parties’ proposed findings of fact and conclusions of law, the relevant authorities, and the record as a whole, the Court finds that Plaintiffs have shown by a preponderance of the evidence that Defendant infringed on the asserted claims (the “Asserted Claims”) in the patents-in-suit, and Defendant has failed to show by clear and convincing evidence that the Asserted Claims of the patents-in-suit are invalid for obviousness, indefiniteness, inadequate description, or lack of enablement. The Asserted Claims of the patents-in-suit are valid and enforceable. For the reasons set forth below, judgment is entered in favor of Plaintiffs and against Defendant, and a permanent injunction shall be entered accordingly.

In support of this decision, the Court makes the following findings of fact and conclusions of law under Rule 52 of the Federal Rules of Civil Procedure. Because the parties raised claim construction disputes on the first day of trial, this Memorandum also construes the several disputed claims. To provide clarity on the disputed claims, the Court begins with some findings of fact (Part II), detours with claim construction (Part III), finishes its findings of fact by describing the evidence the parties presented at trial (Part IV), and concludes with conclusions of law (Part V).

I. LEGAL STANDARD

In a bench trial “tried on the facts without a jury . . . , the court must find the facts specially and state its conclusions of law separately.” Fed. R. Civ. P. 52(a)(1).

The primary purpose of Rule 52(a)(1) is to “aid[] the trial court’s adjudication process by engendering care by the court in determining the facts.” *Garner v. Kennedy*, 713 F.3d 237, 242 (5th Cir. 2013); *see also McKee v. Brunswick Corp.*, 354 F.2d 577, 580 (7th Cir. 1965). The trial court “need only make brief, definite, pertinent findings and conclusions upon the contested matters” such that the findings are “explicit enough to enable appellate courts to carry out a meaningful review.” Fed. R. Civ. P. 52(a)(1) advisory committee’s note to 1946 amendment; *Garner*, 713 F.3d at 243.

II. FINDINGS OF FACT

A. The Parties and Procedural Posture

Plaintiffs are biopharmaceutical companies that develop antibiotics to treat infectious diseases. (Dkt. 252 ¶ 4.) Plaintiffs own New Drug Application No. 050444 (the “NDA”) for the FDA-approved Minocin product. (Dkt. 228-1 ¶ 5.) Plaintiffs own the ’105 Patent and the ’802 Patent, which are both listed in the FDA’s Orange Book¹ in connection with the NDA and Minocin. (Dkt. 228-1 ¶¶ 7, 16–17, 26–27.) The inventors of the patents-in-suit are David C. Griffith, Serge Boyer, Scott Hecker, and Michael N. Dudley. (*Id.* ¶¶ 9, 20.) The priority date of the patents-in-suit is May 12, 2010. (*Id.* ¶¶ 8, 19.)

Defendant Nexus Pharmaceuticals, Inc. is a pharmaceutical company that makes generic versions of FDA-approved injectable drug products. (Dkt. 252 ¶ 7.)

¹ The “Orange Book” is a publication authored by the FDA that “identifies drug products approved on the basis of safety and effectiveness [by the FDA] under the Federal Food, Drug, and Cosmetic Act . . . and related patent and exclusivity information.” *Approved Drug Products with Therapeutic Equivalence Evaluations—Orange Book: Background*, U.S. Food & Drug Admin. (Jan. 25, 2024), <https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book>.

Defendant owns the ANDA, which Defendant submitted to the FDA on October 16, 2020 seeking to develop a generic version of Minocin prior to the expiration of the patents-in-suit. (Dkt. 228-1 ¶ 6.) As part of the ANDA approval process, Defendant sent a notice to Plaintiffs asserting that its ANDA did not infringe the patents-in-suit, or, alternatively, that the patents-in-suit were invalid. (*Id.*) Plaintiffs responded to the notice by filing this lawsuit, which triggered an automatic thirty-month stay² of regulatory approval of Defendant's ANDA. *See* 21 U.S.C. § 355(j)(5)(B)(iii).

Plaintiffs filed this lawsuit on May 14, 2021. (Dkt. 1.) On December 7, 2021, this case was consolidated with related Case No. 21-cv-05995, which was originally filed in the District Court for the District of New Jersey and transferred to this Court on November 5, 2021. (Dkts. 42; 45.) The related case asserts the same claims against Defendant and was, therefore, consolidated to save judicial time and resources. (Dkt. 42.) The cases were consolidated for pretrial and trial matters but were not merged, thereby requiring separate judgments. (Dkt. 45.)

Plaintiffs' complaint contains three counts. (Dkt. 1.) Count I, brought under 21 U.S.C. § 335(j)(5)(B)(iii) and 21 C.F.R. § 314.95, seeks a declaratory judgment to resolve whether the thirty-month stay of FDA approval was triggered. (*Id.* ¶¶ 1, 28–38.) Counts II and III were brought under 35 U.S.C. § 271(e)(2)(A), alleging that Defendant infringed upon the patents-in-suit when Defendant submitted its ANDA seeking approval to engage in the commercial manufacture, sale, use, and/or importation of Defendant's ANDA products before Plaintiffs' patents had expired. (*Id.*

² The stay ended on September 30, 2023. (Dkt. 228 ¶¶ 89–90.)

¶¶ 39–62.) Count II alleges infringement of the '105 Patent and Count III alleges infringement of the '802 Patent. (*Id.* ¶¶ 40, 52.) Defendant filed an answer and counterclaims. (Dkt. 9.) Defendant argues in Count I of the counterclaim that it did not infringe on the '105 Patent because the patent was invalid. (*Id.* ¶¶ 27–31.) Defendant makes identical arguments in Count II of the counterclaim, but for the '802 Patent. (*Id.* ¶¶ 32–36.)

Defendant moved to dismiss Count I of the complaint for lack of subject matter jurisdiction, or, alternatively, for failure to state a claim or under the doctrine of primary jurisdiction. (Dkt. 39.) This motion was stayed pending resolution of a related action in the District of Columbia. (Dkt. 189; Dkt. 192.) *Melinta Therapeutics, LLC v. FDA*, No. 22-2190, 2022 WL 610018 (D.D.C. Oct. 7, 2022). In that case, the court granted Melinta's motion for a temporary restraining order and preliminary injunction, vacated the FDA's approval of the ANDA, and remanded the case to the FDA. *Melinta*, 2022 WL 610018, at *10. Defendant appealed this decision, but the District of Columbia Circuit dismissed the appeal for lack of jurisdiction and agreed that the case should remain remanded to the FDA. *Melinta Therapeutics, LLC v. FDA*, No. 22-5288, 2022 WL 19723218, at *1 (D.C. Cir. Dec. 1, 2022). The parties have since reported that the FDA has approved the ANDA. (Dkt. 271.) Accordingly, Count I is dismissed as moot. Counts II and III of Plaintiffs' complaint, along with Counts I and II of Defendant's counterclaims, proceeded to trial.

A bench trial took place over four days from June 6, 2023 to June 9, 2023. Closing arguments were heard separately on August 15, 2023. Plaintiffs called three

witnesses: (1) Dr. Bruce Friedman (“Dr. Friedman”), (2) Dr. Tina deVries (“Dr. deVries”), and (3) David Griffith (“Griffith”). (Dkt. 228 ¶ 16.) Defendant called two witnesses: (1) Dr. Henry F. Chambers (“Dr. Chambers”), and (2) Dr. Alexander Klibanov (“Dr. Klibanov”). (Dkt. 228 ¶ 18.) After Plaintiffs rested their case, Defendant moved for an oral Rule 52(c) judgment on partial findings in its favor. (Tr. 455:14–16.) The Court took the oral motion under advisement and reserved ruling until the close of evidence. (Tr. 456:3–21.) *See* Fed. R. Civ. P. 52(c). The Rule 52(c) motion is subsumed with the Court’s following evaluation of the case.

After the conclusion of the bench trial, the parties submitted proposed findings of fact and conclusions of law with citations to the record. (Dkts. 252; 253; 255.) Because the issue of claim construction arose during the bench trial, both parties’ proposed findings of fact and conclusions of law include their proposed constructions of several disputed claim terms within the allegedly infringing claims. (Dkt. 252 ¶¶ 45–91; Dkt. 255 ¶¶ 20–41.) The Court begins by first explaining the prior art minocycline, Minocin, and the ANDA product, and then reciting the disputed claims. With an understanding of the products at issue, the Court construes the disputed claims in Part III.

B. Plaintiffs’ Minocin Product

Plaintiffs’ Minocin product replaced an old intravenous (IV) minocycline formulation (the “prior art minocycline”), a product approved in 1972 to treat bacterial infections caused by the *Acinetobacter baumannii* bacteria. (Tr. 75:17, 322:17–323:14; DTX-0027.) The prior art minocycline was removed from the market

in 2005 but returned in 2009 because no other similar product existed to treat bacterial infections. (Tr. 705:8–10, 707:13–708:1.) Around that time, the inventors began research for the patents-in-suit, hoping to improve the prior art minocycline. (Tr. 320:9–22.) A few years later, Plaintiffs acquired the NDA for the prior art minocycline and shortly thereafter filed a supplemental NDA seeking to replace the prior art minocycline with their new Minocin formulation. (Dkt. 255 ¶¶ 10–11; DTX-0072.)

Both the prior art minocycline and Minocin are intended to be administered to a patient intravenously, *i.e.*, injected into the patient’s vein. An intravenous product begins as a powder or other dried substance. But to be administered intravenously, the powder must be dissolved to create an aqueous³ solution. Both the prior art minocycline and Minocin require dissolution—or, in scientific terms, reconstitution—in 5 mL of sterile water. (*See* DTX-110; DTX-112.) The reconstituted liquid solution is then a fully dissolved aqueous solution suitable for intravenous injection. Accordingly, the term “reconstituted solution” used in this Memorandum refers to the drug product dissolved in 5 mL of water before it is further diluted. After reconstitution, the reconstituted solution must be diluted further with an additional diluent to prepare it for intravenous administration. The prior art minocycline label instructs a POSA to further dilute the reconstituted solution in 500 mL to 1,000 mL of a compatible diluent. (DTX-112.) The Minocin label instructs further dilution in 100 mL to 1,000 mL of specific diluents, but the relevant claims in this action instruct

³ “Aqueous” means “of the nature of water.” Aqueous, *Taber’s Medical Dictionary Online* (24th ed.).

an injection volume of “less than 500 mL.” (DTX-110; PTX-1.) The diluted solution is also referred to as the “admixture.”

The inventors of the patents-in-suit set out to improve the prior art minocycline. Although the prior art minocycline effectively treated bacterial infections, it suffered from several faults. First, it had a low pH level. Second, it required a high injection volume. Although Defendant disputes this, the low pH level and high injection volume created a risk of irritability, tolerability, and other injection site hemolysis⁴ issues.

First, the prior art minocycline had a low pH level. A pH level is a “measure of acid intensity,” and the lower the pH level, the more acidic a solution is. (Tr. 611:7–8.) The prior art minocycline pH levels range from 2.0 to 6. The pH level for the reconstituted solution is 2.0 to 2.8, 2.5 to 4 after dilution, and 4.5 to 6 after dilution in a particular diluent called Lactated Ringer’s. (Tr. 328:25–329:5, 480:10–481:3, 611:9–18, 797:18–20, 890:8–17; DTX-112.) Dr. Friedman testified that those prior art minocycline pH levels were low, and that a pH level closer to 7.35 to 7.45 is needed for safe administration to patients. (Tr. 117:7–13.) A pH level that is too low—and therefore more acidic—can trigger injection site hemolysis. (*Id.* at 117:14–20, 117:25–118:14.)

Second, the prior art minocycline required a high injection volume. The prior art minocycline instructed an administration at a volume of at least 500 mL and up to 1,000 mL per infusion. A higher volume was required because more diluent

⁴ The definition of “injection site hemolysis” follows in Section III.C.4 of this Memorandum.

increased the pH level and thus reduced injection site hemolysis. (*Id.* at 119:10–12, 323:25–324:7.) But a high infusion volume would put patients at risk of fluid overload, especially those patients who were already receiving other intravenous fluids. An overload of intravenous fluids then created a risk of other serious medical issues. (*Id.* at 118:15–19:9, 331:2–18.)

These issues caused the prior art minocycline to be used as a last resort before being removed from the market entirely. (Dkt. 252 ¶ 182; Tr. 704:18–05:15.) The product was reintroduced to the market a few years later because no other efficacious product existed to treat bacterial infections, but it continued to suffer from the same problems. Attempts to improve the prior art minocycline were “valiant” but ultimately unsuccessful due to solubility,⁵ stability,⁶ or injection site tolerability issues. (Dkt. 252 ¶ 183; Tr. 325:7–20, 709:17–710:14, 798:14–22.) Solubility was a problem because an intravenous product must be administered as an aqueous solution, and if the product is not completely dissolved, it cannot be intravenously administered safely. Stability was a problem because the minocycline molecule needs to remain unchanged to be effective against the bacteria it is intended to treat. And injection site tolerability issues were a problem because the aqueous formulation needed to be administered intravenously without causing harmful effects to the skin or the blood cells.

⁵ “Solubility” refers to the “capability [of a substance] of being dissolved,” a necessary property of all drugs in order for them to be administered to a patient. Solubility, *Taber’s Medical Dictionary Online* (24th ed.). (See also Tr. 197:20–198:12.)

⁶ “Stability” refers to “the condition of remaining unchanged, even in the presence of forces that would normally change the state or condition.” Stability, *Taber’s Medical Dictionary Online* (24th ed.). (See also Tr. 332:19–333:6.)

The inventors thus set out to improve the prior art minocycline without any solubility, stability, or tolerability issues. The final patented Minocin product differs from the prior art minocycline in one primary respect: the addition of magnesium. The addition of magnesium at a high ratio in relation to minocycline enables the pH of the solution to be adjusted to a more physiologic⁷ range. In turn, if the pH can be adjusted higher, a high injection volume can be decreased because it is no longer needed to improve pH, thereby reducing injection site tolerability issues. (Tr. 121:18–23.) The pH levels for Minocin, according to its label, are as follows: 4.5 to 5.0 for the reconstituted solution, and 4.5 to 6 after dilution in compatible solutions. (DTX-110.) The injection volume for Minocin is 100 mL to 1,000 mL when diluted in various solutions, or 250 mL to 1,000 mL when diluted in Lactated Ringer’s. (*Id.*)

The patents-in-suit elaborate on what the Minocin label states. They describe the use of minocycline (a 7-dimethylamino-tetracycline) with divalent⁸ metal cations⁹. (Tr. 421:9–19; PTX-1; PTX-2.) The particular divalent metal cation specified in the patents-in-suit is magnesium. (*Id.*) The patents-in-suit specify that a higher molar ratio of divalent cations (specifically, magnesium) to a tetracycline (specifically,

⁷ “Physiologic” means “characteristic of or appropriate to an organism’s healthy or normal functioning.” So, the characteristics of solution at a physiologic range are characteristics that match or are similar to those characteristics within an organism such as a human. Physiologic, *Mirriam-Webster Unabridged Dictionary*.

⁸ “Divalent” describes the property of a molecule “having an electric charge of two.” Divalent, *Taber’s Medical Dictionary Online* (24th ed.).

⁹ A “cation” is an “ion with a positive electric charge.” Cation, *Taber’s Medical Dictionary Online* (24th ed.). When used in the context of patient care, a cation is “a positively charged ion[] that contribute[s] to the pH of human plasma.” *Id.* Examples of such cations are calcium, magnesium, potassium, and sodium. *Id.*

minocycline) successfully decreases hemolysis in relation to a formulation like the prior art minocycline that does not have magnesium. (*Id.*) The '802 Patent instructs a molar ratio of magnesium to minocycline that is greater than about 4 to 1, and the '105 Patent one that is greater than 3 to 1. (Tr. 107:15–108:2, 424:13–17; PTX-1 at 40:51–52; PTX-2 at 41:40.)

In addition, the '105 Patent specifies one additional property in its Minocin product. In Claim 1, the patent specifies “an osmolality¹⁰ of less than about 500 milliosmols per kilogram (mOsmol/kg).” (PTX-002 at 41:43.) Osmolality is a measurement that can be calculated by a POSA after reading the ingredients and amounts of those ingredients on a product label. Neither the prior art minocycline label nor the Minocin label specify the osmolality level of their respective products.

C. Defendant’s ANDA

Defendant filed its ANDA on October 16, 2020 seeking approval to develop a generic magnesium-based minocycline product before the expiration of the patents-in-suit, certifying that the patents-in-suit were either invalid or not infringed by the ANDA. (Dkt 228-1 at 1.) Because Minocin is an intravenous product, FDA regulations require generic products such as Defendant’s ANDA to have the same active and inactive ingredients in the same amounts as Minocin. (Tr. 205:21–206:5.) The ANDA

¹⁰ “Osmolality” refers to the “concentration of a solution expressed in osmoles of solute particles per kilogram of solvent.” Osmolality, *Stedmans Medical Dictionary* (2014). Another medical dictionary defines “osmolality” as the “concentration of an osmotic solution by the concentration of the dissolved substances per 100 g [or 1 kg] of solvent.” Osmolality, *Taber’s Medical Dictionary Online* (24th ed.). In other words, osmolality measures (by weight) the concentration of dissolved particles in a solvent. (See Tr. 135:22–24.) The general standard of care for osmolality with respect to IV medications is less than 500 mOsmol/kg. (Tr. 136:15–18, 762:16–19.) A higher osmolality may cause tissue damage. (Tr. 137:10–12.)

describes a minocycline for injection product that contains three ingredients: (1) minocycline, (2) magnesium, and (3) a base. (PTX-042.) Defendant explained in several statements to the FDA that the purpose of magnesium in its ANDA product is reduction of injection site hemolysis. (Tr. 230:9–231:9; *see, e.g.*, PTX-021; PTX-206; PTX-211.) The ANDA does not identify a diluent in the list of ingredients. (*Id.*) But the ANDA label instructs that the composition be diluted in 100 to 1,000 mL of a diluent for adult use. (PTX-042.) According to the ANDA’s label, the pH level of the ANDA composition before dilution is 4.5 to 5. (PTX-028; PTX-042.) After dilution, the pH “usually ranges from 4.5 to 6.0.” (PTX-042.) The label does not specify the ANDA product’s molar ratio or osmolality. The label explains that the ANDA minocycline for injection product is designed with the preceding ingredients and properties for the purpose of treating or preventing bacterial infections. (PTX-042.)

D. The Asserted Claims

1. The ’802 Patent

Plaintiffs first assert infringement of Claims 1, 7, and 18 of the ’802 Patent. (Dkt. 228-1 ¶ 12.) Claim 1 of the ’802 Patent recites:

1. A method of treating a bacterial infection in a subject, wherein the method consists of:

administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration,

wherein the composition consists of an aqueous solution consisting of minocycline or a salt thereof, a salt that comprises a magnesium cation, and a base,

wherein the molar ratio of magnesium cation to minocycline is greater than about 4:1, and

wherein the composition has a pH that is no less than 4 and no greater than 6,

whereby injection site hemolysis of red blood cells is reduced relative to intravenous administration of a composition that does not include magnesium.

(*Id.* ¶ 13.)

Claim 7 of the '802 Patent depends from Claim 1 and recites: "7. The method of Claim 1, wherein the composition has a pH between about 4.5 to about 5.5." (*Id.* ¶ 14.)

Claim 18 of the '802 Patent depends from claim 1 and recites: "18. The method of claim 1, wherein the total volume of the composition administered is less than 500 mL." (*Id.* ¶ 15.)

2. *The '105 Patent*

Plaintiffs next assert infringement of Claim 27 of the '105 Patent, which depends from Claim 1 of the '105 Patent. (*Id.* ¶ 23.) Claim 27 recites: "27. The method of claim 1, wherein the 7-dimethylamino-tetracycline is minocycline." (*Id.* ¶ 25.)

Claim 1 is an unasserted claim, but for clarity, because Claim 27 depends from it, Claim 1 recites:

1. A method of treating a bacterial infection in a subject, wherein the method comprises administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration, wherein the composition comprises an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a magnesium cation, wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and wherein the solution does not comprise a pharmaceutically acceptable oil, has a pH greater than 4 and less than 7, and has an osmolality less than about 500 mOsmol/kg.

(*Id.* ¶ 24.)

III. CLAIM CONSTRUCTION

The claims of a patent are questions of law to be determined by the district court, not a question of fact to be determined by the factfinder. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 384 (1996). This process, dubbed “claim construction,” is the “process of giving proper meaning to the claim language” which then “defines the scope of the protected invention.” *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1023 (Fed. Cir. 1997). Claim construction “frames and ultimately resolves all issues of claim interpretation.” *Id.*

The court typically construes claims and terms within claims before trial, after the parties submit claim construction briefs and the court conducts a claim construction hearing. *See* N.D. Ill. L. Pat. R. 4.1–4.3. But the court’s understanding of claims may change as the trial proceeds. The court can thus engage in “rolling” claim construction, “in which the court revisits and alters its interpretation of the claim terms as its understanding of the [case] evolves.” *Conoco, Inc. v. Energy & Env’t Int’l, L.C.*, 460 F.3d 1349, 1359 (Fed. Cir. 2006) (quoting *Guttman, Inc. v. Kopykake Enters., Inc.*, 302 F.3d 1352, 1361 (Fed. Cir. 2002)).

On March 21, 2022, over one year before the bench trial was held, the parties filed a joint status report stating that “neither Plaintiffs nor Defendant identified any terms requiring construction. Accordingly, the parties agree that no briefing, hearing or claim construction ruling by the Court is necessary.” (Dkt. 70 at 1–2.) But on June 6, 2023, the first day of the bench trial, Defendant informed the Court of a claim construction issue that arose the previous day that was “significant enough to raise”

at trial. (Tr. 3:13–19.) Defendant stated that after reviewing Plaintiffs’ materials, it believed “plaintiffs intend to change the words or add to the words in the claim.” (Tr. 4:8–12.) Plaintiffs denied that they were “arguing or proffering a special meaning of any of the claims,” nor were they “attempting to add words to the claim.” (Tr. 4:18–21.) The Court decided, with the parties’ input and approval, to move forward with the trial, listen to the arguments, and determine after trial whether any claim construction issue persisted. (Tr. 7:17–10:3.) The parties were instructed to object during trial when a claim construction issue arose and file a post-trial motion or brief regarding the claim construction dispute if they deemed it necessary. (Tr. 7:17–10:3.) Both made claim construction objections during trial and presented various claim construction arguments in post-trial briefings. (Dkts. 249; 250; 251; 252; 253; 254; 255.) Accordingly, this Court must engage in post-trial rolling claim construction and will construe the several disputed claims raised by the parties.

A. Legal Standard

Claim construction begins with a “heavy presumption” that words in a claim are given their “ordinary and customary meaning.” *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir. 2002); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The “ordinary and customary meaning” of a claim term is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). The court stands in the shoes of a person of ordinary skill in the art (a “POSA”) and “review[s] the same resources as would” a POSA. *Multiform*

Desiccants, Inc. v. Medzam, 133 F.3d 1473, 1477 (Fed. Cir. 1998). The court, acting as a POSA, reads the claim terms “with an understanding of their meaning in the field” and applies “knowledge of any special meaning and usage [of the terms] in the field.” *Phillips*, 415 F.3d at 1313.

Often, the ordinary and customary meaning of a claim term, even when read from the perspective of a POSA, is “readily apparent” and can be determined with “little more than the application of the widely accepted meaning of commonly understood words.” *Id.* at 1314. In more complex cases, however, “because the meaning of a claim term as understood by [a POSA] is often not immediately apparent, and because patentees frequently use terms idiosyncratically, the court looks to” other sources to define the claim. *Id.* The court primarily looks to intrinsic evidence contained in the record, such as the claims themselves, the patent’s specification, and the patent’s prosecution history. *Id.*

The patent’s claims themselves, along with the context in which the terms appear in the claim, “provide substantial guidance as to the meaning of particular claim terms.” *Id.*; *ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003). Second, the patent’s specification is “highly relevant” because new patents are required to be described in “full, clear, concise, and exact terms.” *Vitronics*, 90 F.3d at 1582; 35 U.S.C. § 112. Accordingly, the construction “that stays true to the claim language and most naturally aligns with the patent’s description of the invention will be, in the end, the correct construction.” *Renishaw PLC v. Marposs Societa’ per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). An exception to this “ordinary and customary

meaning” rule exists when the inventor acts as the patent’s lexicographer and expresses in the specification that a claim term has “a special definition . . . that differs from the meaning it would otherwise possess.” *Phillips*, 415 F.3d at 1316. In such a circumstance, the inventor’s definition is dispositive. *Id.* Third, the patent’s prosecution history, which includes the “complete record of the proceedings before the [United States Patent and Trademark Office (“USPTO”)] and includes the prior art cited during the examination of the patent,” is helpful to claim construction because it provides insight into how the USPTO and inventor understood the patent and accurately represents what the patentee intended with the patent. *Id.* at 1317.

District courts are also authorized to look to extrinsic evidence such as dictionaries, treatises, and expert testimony to determine the “ordinary and customary meaning” of a claim term. *See id.* at 1317–18 (quoting *Markman*, 52 F.3d at 980). But the use of extrinsic evidence should be limited. Extrinsic evidence may not contradict the intrinsic evidence. *See Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1382 (Fed. Cir. 2008). Because extrinsic evidence is removed from the facts of the patent in question, it is less reliable than intrinsic evidence; extrinsic evidence should therefore only be “considered in the context of the intrinsic evidence.” *Phillips*, 415 F.3d at 1319.

B. Person of Ordinary Skill in the Art

Because patent claims are construed from the perspective of a POSA, the Court must begin its claim construction analysis by defining who a POSA is in this case. A POSA is a hypothetical person “deemed to read the words used in the patent

documents with an understanding of their meaning in the field, and to have knowledge of any special meaning and usage in the field.” *Id.* at 1313 (citing *Multiform Desiccants, Inc.*, 133 F.3d at 1477). A POSA is presumed to be aware of all pertinent prior art, regardless of whether the patentee is actually aware of the existence of all prior art. *See Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985).

The parties disagree slightly on the proper definition of a POSA. Plaintiffs’ expert Dr. deVries testified that a POSA is “a chemist, a formulator, a pharmaceutical scientist or infectious disease or critical care doctor with an advanced degree and experience with chemistry, formulation, and / or administration of tetracyclines [who] . . . would collaborate with other POSAs as necessary.” (Tr. 203:22–204:3.) Defendant’s expert Dr. Klibanov testified that a POSA is an “individual with an advanced degree in pharmacy, chemistry, or a related field, plus practical experience with pharmaceutical formulations, including their methods of preparation, stability, characterization, and administration, along with a physician or a medical professional who administers injectable formulations.” (Tr. 463:11–17.) The key difference between these proposed definitions is whether the POSA has experience working with tetracyclines. Both experts, however, stated that their opinions would not change if they applied the opposing party’s definition of a POSA. (Tr. 204:8–11, 464:3–5.) Accordingly, this Court defines a POSA in this case with elements that are common to both parties: “an individual with an advanced degree in chemistry,

pharmacy, or a related field, and with experience in pharmaceutical formulations and administrations.”

C. The Disputed Claim Terms

1. “Composition”

The parties first dispute the claim term “composition.” This claim term appears multiple times in Claim 1 of the ’802 Patent, which reads (with the relevant claim term underlined):

1. A method of treating a bacterial infection in a subject, wherein the method consists of:

administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration,
wherein the composition consists of an aqueous solution consisting of minocycline or a salt thereof, a salt that comprises a magnesium cation, and a base,
wherein the molar ratio of magnesium cation to minocycline is greater than about 4:1, and
wherein the composition has a pH that is no less than 4 and no greater than 6,
whereby injection site hemolysis of red blood cells is reduced relative to intravenous administration of a composition that does not include magnesium.

The claim term also appears in Claims 7 and 18 of the ’802 Patent, which depend on claim 1. Claim 7 reads: “The method of claim 1, wherein the composition has a pH between about 4.5 to about 5.5.” Claim 18 reads: “The method of claim 1, wherein the total volume of the composition administered is less than 500 ml.” Claim 27 of the ’105 Patent also includes the word “composition,” because it depends on Claim 1. Claim 27 reads: “The method of claim 1, wherein the 7-dimethylamino-tetracycline is minocycline.” And Claim 1 reads:

1. A method of treating a bacterial infection in a subject, wherein the method comprises administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration, wherein the composition comprises an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a magnesium cation, wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and wherein the solution does not comprise a pharmaceutically acceptable oil, has a pH greater than 4 and less than 7, and has an osmolality less than about 500 mOsmol/kg.

In their post-trial briefings, Plaintiffs extensively argue that the plain and ordinary meaning of “composition” is the concentrated, reconstituted solution in the vial prior to dilution. (Dkt. 249 at 3.) Plaintiffs explain that everywhere the term “composition” is mentioned in the claims, it is in reference to the solution before dilution. (*Id.*; Dkt. 251 at 3–4.) In one place, “composition” is followed by a list of ingredients, none of which are a diluent. (Dkt. 249 at 3.) It follows, then, according to Plaintiffs, that “composition” includes only the listed ingredients before a diluent is added. (*Id.*) Plaintiffs’ expert witnesses testified at trial that a POSA would agree, based on the patent’s specification, that “composition” refers to the reconstituted solution before dilution. (Tr. 103:2–19; 217:19–218:10, 19–24.) In post-trial briefings, Plaintiffs emphasize that it is undisputed that the Asserted Claims are specific only to minocycline “compositions”—not all “compositions” in the specification—and the references to minocycline compositions in the specification do not include a diluent. (Dkt. 251 at 3–4.) Plaintiffs also cite the pH levels stated in the patents as further support for their proposed construction of “composition,” arguing that all references to the pH of the “composition” in the patent specifications is to the pH levels of the reconstitute solution before adding a diluent. (Dkt. 249 at 4; Dkt. 252 ¶¶ 46–49.)

Defendant disagrees. Defendant argues that the plain and ordinary meaning of “composition” is whatever is administered to a patient. (Dkt. 250 at 16; Dkt. 254 at 8–10.) Defendant cites the patent specifications, which state that “composition” refers to what is administered—and because the solution can only be administered *after* it is diluted, “composition” must mean the diluted solution. (*Id.*)

The Federal Circuit has long viewed the term “composition” as a term of art in chemistry and patent law and has regularly interpreted a chemical “composition” to exist “at the moment the ingredients are mixed together. Before the creation of the mixture, the ingredients exist independently.” *Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1558 (Fed. Cir. 1995). Consequently, a patentee’s claims are a “composition that contains the specified ingredients at any time from the moment at which the ingredients are mixed together. This interpretation of [the patentee’s] claims preserves their identity as product claims, and recognizes as a matter of chemistry that the composition exists from the moment created.” *PIN/NIP, Inc. v. Platte Chem. Co.*, 304 F.3d 1235, 1244 (Fed. Cir. 2002) (quoting *Exxon*, 64 F.3d at 1558); *see also Mars, Inc. v. H.J. Heinz Co., L.P.*, 377 F.3d 1369, 1374 (Fed. Cir. 2004); *Kim v. The Earthgrains Co.*, 2005 WL 66071, at *11 (N.D. Ill. Jan. 11, 2005) (construing “composition” in the patent as the “specific ingredients . . . at any time from the moment they are mixed together”).

Applying this standard, the plain and ordinary meaning of “composition” refers to the specified ingredients stated in the claim the moment they are mixed together. There are three specified ingredients in Claim 1 of the ’802 Patent: “an aqueous

solution consisting of minocycline or a salt thereof, a salt that comprises a magnesium cation, and a base.” (PTX 1 at 40:48–50.) And there are two specified ingredients in Claim 1 of the ’105 Patent: “an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a magnesium cation.” (PTX 2 at 41:37–48.) A diluent is not mentioned in either. The “composition” thus means the three ingredients specified in Claim 1 of the ’802 Patent claims and the two ingredients specified in Claim 1 of the ’105 Patent at the moment they are mixed, without a diluent.

The ’802 Patent and ’105 Patent specifications do not, as Defendant contends, provide a basis for deviating from this plain and ordinary meaning. The word “composition” is used many times throughout the specifications, but the Asserted Claims in the case are directed in particular to the minocycline “compositions” mentioned in the specifications. (Tr. 203:13–18.) The four minocycline compositions in the specifications do not include a diluent in the list of ingredients. (PTX-1 at 3:38–55; PTX-2 at 3:32–49.) Defendant cites to several places in the specifications that allegedly prove the existence of a diluent in the “composition,” but the examples Defendant points to are not specifically minocycline “compositions,” and they do not say anything about a diluent as an ingredient. (See Dkt. 250 at 16; PTX-1 at 6:26–36, 12:13–34.) None of the minocycline “compositions” in the specifications provide any basis for deviating from the plain and ordinary meaning of the phrase “composition.” Defendant does not argue that the prosecution history suggests otherwise.

Based on this construction, the Court agrees with Plaintiffs that all references in the specifications to the pH of the composition describe the pH of the reconstituted

solution without a diluent. All pH references in the specifications follow an ingredient list (none of which include a diluent) or explicitly say that the stated pH level is “the pH of a reconstituted solution.” (PTX-1 at 3:38–4:24, 14:46–15:56, 38:1–39:55; PTX-2 at 3:32–4:18, 14:32–15:42, 38:59–40:45.)

For these reasons, this Court holds that the term “composition” as used in Claims 1, 7, and 18 of the ’802 Patent refers to the three ingredients—minocycline, magnesium, and a base—explicitly listed in the claims at the moment the ingredients have been mixed together. In Claims 1 and 27 of the ’105 Patent, the claim term “composition” refers to the two ingredients—minocycline and magnesium—explicitly listed in Claim 1 at the moment the ingredients have been mixed together. It therefore follows that the pH level of the “composition” stated in the claims is the pH level of the reconstituted solution without a diluent.

2. “Consists / consisting of”

The second disputed claim term is “consists of” or “consisting of.” This claim term is closely related to “composition.” The terms are adjacent to one another in Claim 1 of the ’802 Patent: “. . . wherein the composition consists of an aqueous solution consisting of minocycline or a salt thereof, a salt that comprises a magnesium cation, and a base” Like “composition,” the parties dispute whether the claim term “consists / consisting of” includes a diluent.

Diverting from its position on the term “composition,” Defendant argues that “consists / consisting of” *does not* include a diluent. Defendant argues that the claim

term “consists / consisting of” can only refer to the three ingredients that are listed in the patent (minocycline, magnesium cation, and a base). (Dkt. 250 at 16–18.)

Plaintiffs do not explicitly construe “consists / consisting of,” and only mention the claim term in their post-trial briefings to respond to Defendant’s proposed construction. Plaintiffs argue that Defendant’s construction of “consists / consisting of” is at odds with its proposed construction of “composition.” (Dkts. 249 at 5–6; 251 at 5–6.) It is Plaintiffs’ position that Defendant’s constructions of “composition” and “consists / consisting of” cannot both be correct. (Dkt. 251 at 5–6.) According to Plaintiffs, if Defendant is correct that “composition” *does* include a diluent, but “consists / consisting of” *does not* include a diluent, the patent could never be infringed—which “cannot be correct.” (Dkts. 249 at 5–6; 251 at 5–6.)

Like “composition,” the claim term “consists of” or “consisting of” is a well-established term of art in patent law. The Federal Circuit has repeatedly held that the phrase “consists of” or “consisting of” is generally understood to be a closed phrase that excludes any element, step, or ingredient not specified in the claim. *See Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1331 (Fed. Cir. 2004) (“ ‘Consisting of’ is a term of patent convention meaning that the claimed invention contains only what is expressly set forth in the claim.”). *See also, e.g., Shire Dev., LLC v. Watson Pharms., Inc.*, 848 F.3d 981, 984 (Fed. Cir. 2017); *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1358 (Fed. Cir. 2016); *AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 239 F.3d 1239, 1245 (Fed. Cir. 2001); *Ga.-Pac. Corp. v. U.S. Gypsum Co.*, 195 F.3d 1322, 1327–28 (Fed. Cir. 1999). This general presumption can

be overcome if the specification and prosecution history “unmistakably manifest an alternative meaning.” *Shire Dev., LLC*, 848 F.3d at 984 (quoting *Multilayer Stretch*, 831 F.3d at 1359).

Claim 1 of the ’802 Patent uses the phrases “consists of” and “consisting of” to list three ingredients in the composition. The ingredients listed in the claim are minocycline, magnesium, and a base. Applying the Federal Circuit’s precedent, this Court construes “consists / consisting of” to mean those three ingredients and to exclude all other ingredients. Neither party argues that the specification or patent history manifests an alternative meaning.

This construction of both “composition” and “consists of / consisting of” is supported by the fact that, as Plaintiffs argue, an alternative claim construction construing “composition” to include a diluent and “consists / consisting of” to not include a diluent would render the claim incoherent and “nonsensical.” (Dkt. 251 at 6.) *See Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014). To simultaneously hold, as Defendant argues, that “composition” includes a diluent but that “consists / consisting of” does not include a diluent is inconsistent at best, because both terms describe the same list of ingredients. Such a construction also “renders the claimed invention inoperable,” as it would be impossible for the invention to work, much less be infringed. *AIA Eng’g Ltd. v. Magotteaux Int’l S/A*, 657 F.3d 1264, 1278 (Fed. Cir. 2011) (quoting *Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 275 F.3d 1371, 1376 (Fed. Cir. 2002)). The Court views such a construction with “extreme skepticism” and thus rejects Defendant’s construction. *Id.* at 1278.

These constructions are consistent with the language of the claims, the patents' specifications, and Federal Circuit precedent, and the Court is not "redrafting" these claim terms in coming to these conclusions, as Defendant suggests. (Dkt. 250 at 17–18.) *See Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004).

3. "Administering"

The parties next dispute the term "administering." The term "administering" is related to both "composition" and "consists / consisting of." The term is used once in Claim 1 of the '802 Patent to describe the method of using the composition: "...wherein the method consists of: administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration" (PTX 1.) The term is used similarly in Claim 1 of the '105 Patent: "... wherein the method comprises administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration" (PTX-2.) The parties' claim construction dispute with the term "administering" is, like "composition" and "consists / consisting of," whether the act of administering the composition includes dilution.

Although Plaintiffs construe "composition" to not include a diluent, Plaintiffs construe "administering" to mean delivering the "composition" to the patient with a diluent. (Dkt. 249 at 4; Dkt. 251 at 2–3.) Plaintiffs argue that since the claims "recite administering the composition intravenously," a POSA would recognize that "administering" the solution through an intravenous route is a "one-step process" involving the mixing of a diluent into the reconstituted solution to ready it for

intravenous administration to the patient. (Dkt. 249 at 4; Tr. 100:10–16, 102:12–103:1.) A POSA would know that the solution could not be administered intravenously by itself without a diluent. (Dkt. 249 at 4; Dkt. 251 at 3.) Accordingly, “administering” must involve a diluent; otherwise, the claim would describe an unusable product.

Elaborating on its construction of “consists / consisting of,” Defendant argues that because its proposed construction of that claim term does not include a diluent, the claim term “administering” also does not involve a diluent. Defendant asserts that the term “administering” means the injection into a patient of the reconstituted solution without a diluent. (Dkt. 250 at 15–16.) Plaintiffs object to Defendant’s construction of this term by pointing out Defendant’s inconsistency in arguing that “composition” means the three ingredients plus a diluent, yet also arguing that “administering” the composition does not include a diluent (Dkt. 249 at 6.) Plaintiffs conclude that such a construction cannot be correct, because under Defendant’s constructions of these claim terms, no one could ever possibly follow the patent’s specification—therefore, infringement too would be impossible. (Dkt. 249 at 6.)

The word “administer” is a “[c]ommon English word” understood by any ordinary person. *ecoNugenics, Inc. v. Bioenergy Life Sci., Inc.*, 355 F. Supp. 3d 785, 795 (D. Minn. 2019). A lay judge can therefore easily conclude that the plain and ordinary meaning of the word is, in the medical sense, “ ‘to introduce into or ingest’ a medication.” *Id.* According to Miriam-Webster’s unabridged dictionary, “administer” means “to give remedially (as in medicine).” *Administer*, Miriam-Webster Unabridged

Dictionary. That definition, in combination with the term as it is used in the patent claims, informs the Court that “administering” means “to give the composition remedially.” The exact method, however, of “administering” the composition requires looking at the patent claims and specifications from the perspective of a POSA.

As to claim language, Claim 1 of the patents-in-suit specifies that the composition is to be administered “intravenously.” (PTX-1; PTX-2.) The claims explain that the “administering” of the composition is for the purpose of “treating a bacterial infection.” (*Id.*) The patent specifications, in turn, repeatedly specify that “administering” must be done “via an intravenous route” or “intravenously.” (*Id.*) The specifications also explicitly discuss the addition of a diluent to prepare the solution for intravenous administration: “To prepare an admixture, sufficient reconstituted solution is mixed in an intravenous bag containing a pharmaceutically acceptable diluent.” (PTX-2 at 13:23–42.) The specification continues, stating that once the reconstituted solution is mixed with a diluent, the “solution is ready for administration.” (*Id.*; *see also* Tr. 219:6–22.)

That the composition is to be administered intravenously is an important consideration. It implies that the composition can be administered to a patient only by a POSA who knows how to administer medication intravenously. Exactly how a POSA would intravenously give the composition to a patient is therefore relevant. For example, in *Shire LLC v. Amneal Pharms.*, No. 11-3781, 2013 WL 4045622 (D.N.J. Aug. 8, 2013), the court held that the defendants’ proposed construction of “administering” an oral medication did not mean “physically delivering into the body

of the patient” because the patents did not envision physical delivery of the medication to a patient by a physician. *Id.* at *17–19. That court noted that if the medication were one that was “given intravenously, there might be a case” for defendant’s proposed construction. *Id.* at *17. This case is distinct from *Shire LLC* because the patents-in-suit do envision physical—specifically, intravenous—delivery of the composition into a patient. Accordingly, the Court must consider how a POSA is to safely deliver the composition to a patient intravenously.

At trial, the expert witnesses confirmed the method of intravenously administering the composition to treat a bacterial infection. Dr. Friedman testified that to use the composition, a POSA would “take th[e] reconstituted solution and mix it into an appropriate diluent, which will then be provided for intravenous administration to the patient.” (Tr. 102:20–23.) He continued, confirming that the reconstituted solution must “be further diluted” before being administered to a patient. (Tr. 102:24–104:25; *see also id.* 436:23–437:6, 720:1–10.) Plaintiffs’ second expert witness Dr. deVries then testified that the “admixture” of the composition plus a diluent “is what is administered or injected into the vein of the patient.” (Tr. 219:21–22.) Defendant’s expert witness Dr. Chambers testified on cross-examination that the composition could not be administered “in any way directly to a patient” without first being “further diluted in a diluent.” (Tr. 675:8–676:4.) The testimony of these three expert witnesses strongly indicates that a POSA would understand that proper administration of the aqueous solution would require dilution of the composition before intravenously injecting it into a patient’s vein.

The Court sympathizes with Defendant’s argument for the exclusion of a diluent in administration, because the claim language in both patents does not mention a diluent. But with due respect to Defendant’s position, the Court cannot agree that “administering” excludes a diluent. The intrinsic evidence demonstrates that the meaning of “administering” cannot begin and end with the words in these claims. First, the language of Claim 1 in the patents-in-suit states that the purpose of the claimed invention is to “treat[] a bacterial infection.” The composition can only effectively treat a bacterial infection if diluted. Second, both the specifications and the claim language require the composition to be administered intravenously. The composition can only be intravenously administered to a patient if diluted. Third, the specifications contemplate the mixture of a diluent with the composition before intravenous administration. Fourth, the trial testimony of three expert witnesses (all of whom would qualify as a POSA) confirmed the necessity of diluting the composition before it can be safely administered to a patient. Examining this intrinsic and extrinsic evidence, this Court holds that diluting the composition is a necessary prerequisite to “administering” the composition and is therefore included in the construction of that claim. *See, e.g., Hospira, Inc. v. Amneal Pharms., LLC*, 285 F. Supp. 3d 776, 803 (D. Del. 2018) (quoting *Phillips*, 415 F.3d at 1314) (although the claim language did not explicitly specify the storage condition of a pharmaceutical composition, the term “administration” included storage condition because “even a lay judge can recognize that proper storage of a pharmaceutical is a prerequisite to administering the pharmaceutical intravenously to a patient”).

The Court’s construction does not divert from the plain and ordinary meaning of the word “administering,” which is, as stated earlier, “to give remedially.” Indeed, the Court’s construction still means “to give remedially.” *Cf. ecoNugenics, Inc.*, 355 F. Supp. 3d at 795–96 (rejecting a proposal to construe “administer” as “make available,” “provide,” “market,” or “sell” and instead construing the term in its “obvious and ordinary meaning” of “to introduce into or ingest” a medication). This construction merely recognizes that the composition cannot be given remedially to a patient consistent with the patent claims and specifications without the use of a diluent. A POSA would read the patent claims and specifications and know to add a diluent to the composition for safe and effective intravenous administration. In short, the composition can only be “given remedially”—or “administered”—intravenously if diluted. This conclusion is supported by the intrinsic and extrinsic evidence and does not divert from the plain and ordinary meaning of the word “administering.” Accordingly, this Court holds that “administering” means “to remedially give the diluted composition to a patient via an intravenous route.”

4. “*Injection Site Hemolysis*”

The parties also dispute the term “injection site hemolysis,” which appears once in Claim 1 (and, therefore, in Claims 7 and 18) of the ’802 Patent: “A method of treating a bacterial infection in a subject . . . whereby injection site hemolysis of red blood cells is reduced relative to intravenous administration of a composition that does not include magnesium.” (PTX-1.)

Plaintiffs argue that the plain and ordinary meaning of “injection site hemolysis” is “damage to red blood cells . . . that is caused by intravenously administered formulations, which in turn causes a cascade of events that can clinically manifest near the injection site . . . in various ways including, for example, phlebitis (skin inflammation), erythema (redness), skin damage / necrosis, thrombophlebitis (swelling / clot in the vein), and pain.” (Dkt. 249 at 7; Dkt. 252 ¶ 62–63.) Plaintiffs add that a “POSA would understand the ‘injection site’ region to be the area around or above where the intravenous port enters the skin and goes into the vein, and ‘injection site hemolysis’ also includes issues downstream due to blood flow.” (Dkt. 249 at 7; Dkt. 252 ¶ 63.)

Plaintiffs argue that the ’802 Patent’s specification supports this definition. For instance, the specification states, “hemolysis can lead to venous phlebitis at the site of injection when administered intravenously, resulting in irritation” (Dkt. 249 at 7; Dkt. 252 ¶ 66.) A POSA would be able to recognize the signs and symptoms of injection site hemolysis and how to reduce the risk after reading the patent’s specification. (Dkt. 249 at 7–8; Tr. 115:3–116:3.)

Defendant’s view on the claim term “injection site hemolysis” is that it is indefinite and undefined. (Dkt. 254 at 10–11.) This view is stated through Dr. Klibanov’s testimony: “the claim term ‘injection site hemolysis’ is somewhat vague, in that there is no teaching in the asserted patents how to measure it, how to know whether the injection site hemolysis is reduced or not.” (Tr. 505:6–9.) Dr. Chambers agreed with this view, testifying that “injection site hemolysis” is not a defined term

in the medical field and does not have an agreed meaning across drug usage. (Tr. 595:2–597:8.) He added that “injection site hemolysis” is also not defined in the patent’s specification, much less a method of determining or measuring its occurrence. (Tr. 596:21–597:8.)

Defendant accurately argues that “injection site hemolysis” is not a defined medical term. “Hemolysis” is a scientific term meaning the “destruction of red blood cells.” *Hemolysis*, Taber’s Medical Dictionary Online (24th ed.); *Hemolysis*, Stedmans Medical Dictionary. “Injection site” is a term a POSA would understand to mean the region around or above where the intravenous port enters the skin and goes into the vein. (See Tr. 113:24–115:17, 696:5–25.) But the term “injection site hemolysis” is not one with a “plain and ordinary meaning” in the medical field. Accordingly, the Court will turn to the ’802 Patent’s claim language and specification to determine the plain and ordinary meaning of the claim term.

The claim language only mentions “injection site hemolysis” once, to explain that the method in the claimed invention reduces injection site hemolysis “relative to intravenous administration of a composition that does not include magnesium.” (PTX 1.) The patent specification does not use the term “injection site hemolysis” at all, but it does use “hemolysis” often. Most references to “hemolysis” in the specification describe hemolysis rates of rabbit red blood cells when experiments were conducted. (*Id.*) One pertinent mention of “hemolysis” connects the term to intravenous injection of the solution. (*Id.* at 1:61–67.) The specification describes the background of the invention, explaining that tetracyclines (such as minocycline) cause tetracycline-

induced hemolysis, which can “lead to venous phlebitis at the site of injection when administered intravenously, resulting in irritation and potentially limiting the volumes of infusion that can be tolerated.” (*Id.*) The specification continues, “It was unexpectedly discovered that the incidence of tetracycline-induced hemolysis can be greatly decreased by formulating the tetracycline with divalent or trivalent cations.” (*Id.* 7:31–33.) These references to “hemolysis” in the specification lead the Court to conclude that “injection site hemolysis” is intended to describe hemolysis that results from the intravenous administration of the composition, which can be noticed by a POSA when the injection site shows phlebitis (inflammation), swelling, redness, or other symptoms familiar to a POSA.

The parties appear to be less concerned about the meaning of “injection site hemolysis” and more concerned about the lack of instruction on how to measure its occurrence or reduction. Dr. Klivanov and Dr. Chambers expressed this concern in their testimony. (Tr. 505:6–9, 595:2–597:8.) Plaintiffs respond by citing data in the ’802 Patent specification and prosecution history from experimental models that directly measured injection site hemolysis, examined injection site reactions, and examined the effect of the formulation on other cell types. (Dkt. 249 at 8; Tr. 223:11–226:22, 344:13–346:15; PTX-71; PTX-196.) These *in vivo*¹¹ and *in vitro*¹² experiments were conducted in solutions containing minocycline and metal cations, and in

¹¹ “*In vivo*” is a scientific term referring to a “laboratory study performed on whole, living organisms, usually animals (including humans) and plants as opposed to a partial or dead organism.” *In vivo*, Taber’s Medical Dictionary Online (24th ed.).

¹² “*In vitro*” is a scientific term referring to a “laboratory study performed on isolated tissue, organs, or cells outside their normal context, as proteins in solution, or cells in an artificial culture medium.” *In vitro*, Taber’s Medical Dictionary Online (24th ed.).

solutions of prior art minocycline (without metal cations) and then compared. (Dkt. 249 at 8.) The experiments showed reduced hemolysis in the solutions containing minocycline and metal cations. (*Id.*) According to Plaintiffs, a POSA would understand this data to show that reduced incidence or risk of injection site hemolysis occurred in a solution containing minocycline and a metal cation. (*Id.*) With this understanding, a POSA would be able to accurately measure the occurrence and reduction of injection site hemolysis in a patient.

Defendant disagrees that the results of these experiments are appropriate benchmarks. They argue that because none of the experiments were performed in live humans, they cannot be used in construing the claim term “injection site hemolysis,” a term used in a patent for a drug to be used in live humans. (Dkt. 249 at 11; Tr. 597:18–600:1.) Plaintiffs respond by citing a prior art reference justifying the use of in vitro tests as a valid model for measuring hemolysis in live patients. (Dkt. 249 at 10; Tr. 835:9–23; PTX 177.) See D.M. Hoover et al, *Comparison of in Vitro and in Vivo Models to Assess Venous Irritation of Parenteral Antibiotics*, 14 FUNDAMENTAL & APPLIED TOXICOLOGY 589 (1990).

The Court agrees with Plaintiffs. The '802 Patent specification discusses the signs and symptoms of hemolysis at the injection site, and the experimental data cited in the specification provides a plethora of evidence for a POSA to assess the occurrence and reduction of hemolysis in a patient. Defendant's concern for the applicability of the in vitro experimental models is unpersuasive, because a POSA would be aware that the in vitro experimental models cited in the specification are

reliable and well-known in scientific literature for evaluating injection site hemolysis. (Tr. 123:24–124:3, 124:5–8, 124:24–125:2, 223:11–225:15, 226:23–227:3, 357:4–10.) A POSA would also be aware of the Hoover article cited by Plaintiffs, which was published well before the patents-in-suit were filed and explicitly concludes that in vitro hemolysis tests like the ones Plaintiffs conducted are valid models for measuring hemolysis in humans. *See* Hoover et al., at 597 (“The coordinated use of these in vitro and in vivo models to evaluate venous irritancy may assist preclinical assessment of potential clinical reactions to new parenteral drug formulations.”). A POSA therefore would have sufficient information to determine how to measure the occurrence and reduction of hemolysis when using this product.

The understood meanings of “hemolysis” and “injection site,” in combination with the ’802 Patent specification’s references to “hemolysis” and what a POSA would know about measuring the occurrence and reduction of hemolysis leads the Court to adopt the Plaintiffs’ proposed definition of “injection site hemolysis.” (Dkt. 249 at 7.) Accordingly, this Court construes “injection site hemolysis” to mean “damage to red blood cells that is caused by intravenously administered formulations, which in turn causes a cascade of events that can clinically manifest near the injection site (or downstream therefrom in the blood) in various ways, including, for example, phlebitis, erythema, skin damage / necrosis, thrombophlebitis, and pain.”

5. “Subject”

The parties next dispute the claim term “subject.” The term “subject” appears once in Claim 1 (and, therefore, in Claims 7 and 18) of the ’802 Patent and once in

Claim 1 (and, therefore, in Claim 27) of the '105 Patent: “A method of treating a bacterial infection in a subject . . .” (PTX-1; PTX-2.) Plaintiffs argue that a “subject” can only be a human, but Defendant argues that “subject” means any animal, including humans. Plaintiffs do not construe this term in post-trial briefings. At trial, however, when Dr. Friedman stated that “subject” means “a human,” Defendant objected, and Plaintiffs’ counsel explained that he did not think “subject” was a claim construction issue. (Tr. 98:22–99:23.) Plaintiffs’ counsel explained that “subject” was defined in the opening report and the patent’s specification and was “not something that’s new, nor is it claim construction.” (Tr. 99:18–23.)

Defendant does address the term “subject” in its post-trial briefings. According to Defendant, “subject” means any animal, including humans. (Dkt. 250 at 18.) Defendant argues that the term cannot be limited to humans because the term “human” is used later in the specification. (*Id.*; see PTX-1 at 37:6–15.) Therefore, if the patentee truly meant for “subject” to be limited to humans, the patentee would have used “human” instead of “subject” in this instance. (*Id.*) Accordingly, Defendant argues, “subject” must include all animals in addition to humans.

The Court construes “subject” to match Defendant’s construction: “any animal, including humans.” The intrinsic evidence cited by Defendant, specifically the '802 Patent and '105 Patent specifications, reveal that the term “subject” should not be limited only to humans. Nowhere in the patent specifications does the patentee express that the composition is to be administered only to human subjects. The term “subject” appears repeatedly throughout the specifications to define the purpose of

the invention (to “treat[] or prevent[] a bacterial infection in a subject”) and to explain how the invention could be administered (either “to the subject via a topical route” or “to the subject via an intravenous route”). (PTX-1 at 6:26–51, 19:15–35, 40:43–47; PTX-2 at 6:19–43, 19:3–25, 41:33–36.) Nothing in that language suggests that “subject” is to be limited to humans. The patent specifications do not provide any additional context implying that “subject” is to refer only to humans. On the contrary, the specifications imply the opposite, since all experiments cited in the specifications were conducted on non-humans (specifically, rabbit and sheep red blood cells). (PTX-1; PTX-2). A POSA reading the claim term in the context of the specifications would not, therefore, have any reason to think that “subject” was limited to “humans.” Accordingly, this Court holds that “subject” is construed to mean “any animal, including humans.”

6. *“Does not include magnesium”*

The final claim construction dispute is the claim term “does not include magnesium.” This term appears once in Claim 1 (and, therefore, in Claims 7 and 18) of the ’802 Patent: “A method of treating a bacterial infection in a subject, . . . whereby injection site hemolysis of red blood cells is reduced relative to intravenous administration of a composition that does not include magnesium.” (PTX-1.)

Defendant construes the claim term in its post-trial briefing, arguing that the claim term should be construed to mean exactly what it says: “does not include magnesium.” (Dkt. 250 at 18–19; Dkt. 254 at 10–11.) Defendant then alleges that Plaintiffs are misconstruing the term to mean “does not include magnesium *or*

another metal cation.” (*Id.*) Defendant explains that if the patentee wanted to include other metal cations in this claim term, it would have done exactly that. (*Id.* at 10.) But because the patentee only used the word “magnesium,” the claim term must be limited to only magnesium. (*Id.*)

In Plaintiffs’ post-trial briefing, they respond that “does not include magnesium” refers to a comparison between the composition and prior art minocycline formulations without metal cations. (Dkt. 251 at 7.) Plaintiffs further argue that all experiments cited in the intrinsic evidence also compare minocycline formulations with metal cations (such as magnesium) to minocycline formulations without metal cations. (*Id.*) Presumably, then, Plaintiffs are arguing for a broadened construction of the claim term—apparently arguing that “does not include magnesium” actually means “does not include any metal cation.”

The construction of this claim term was also mentioned briefly at trial. Defendant objected on claim construction grounds to a question asked to Dr. Friedman regarding this claim term, and Dr. Friedman’s answer appeared to equate “magnesium” to “metal cations.” (Tr. 122:20–123:15.) On cross-examination, when Defendant pressed the issue, Dr. Friedman would not say whether the term “magnesium” necessarily excluded all other metal cations, but he did confirm that magnesium is the particular metal cation that the inventors chose to include in their invention, “the only metal cation that’s in the solution,” and the only metal cation in Defendant’s product. (Tr. 146:17–154:5.)

The Court agrees with Defendant's construction. In some cases of claim construction, the "ordinary meaning of claim language . . . may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Philips*, 415 F.3d at 1314. Such is the case here. The plain and ordinary meaning of "does not include magnesium" describes a formulation that does not include magnesium. The exclusion of any other metal cations is not expressed in any way in the claim language. Plaintiffs used the term "metal cation" in numerous places throughout the patent specification yet chose to limit the claim term to "magnesium." And Plaintiffs' own expert witness confirmed that magnesium is the metal cation specifically chosen to be used in the invention, the only metal cation in the solution. The Court cannot agree with Plaintiffs' interpretation that "does not include magnesium" should be construed to exclude magnesium *and* any other metal cation. Accordingly, "does not include magnesium" is construed to mean "does not include magnesium."

IV. CONTINUED FINDINGS OF FACT: EVIDENCE PRESENTED AT TRIAL

A. The Testifying Witnesses

Five witnesses testified over the course of the trial. As for the credibility of each testifying witness, the Court did not find any witness to lack credibility. Each witness provided believable testimony and did not express any hallmarks of hiding facts or twisting the truth. Instead, any differing testimony about a variety of issues was due to a difference in opinions, which were likely sincerely held by each witness. The Court finds no reason to question the testimony of each witness. What follows in

this Section is an introduction to each testifying witness, and the following Sections describe the expert witnesses' testimony on infringement and invalidity of the Asserted Claims.

1. *Dr. Bruce Friedman*

Plaintiffs' expert witness Dr. Bruce Friedman testified as an expert in infectious disease complications in critically ill patients, including in the clinical knowledge, use, and administration of tetracycline antibiotics, and in particular the clinical knowledge, use, and administration of intravenous minocycline to patients with infectious diseases. (Tr. 85:22–86:3.)

Dr. Friedman is a medical doctor, professor of internal medicine and anesthesiology, and clinical researcher. He has been practicing for forty years and currently works at a burn and wound hospital. (Tr. 72:15–25.) Dr. Friedman's field of expertise is intensive care medicine with a specialty in burn and wounds, which includes significant work with infectious diseases. (Tr. 84:9–18.)

Dr. Friedman testified that he regularly treats patients with skin injuries, which are often injuries that lead to infectious disease complications. (Tr. 73:6–19.) To treat these patients, Dr. Friedman regularly administers intravenous minocycline to them, which he testified was a very effective medication, and he regularly has four to eight patients on minocycline in any given week. (Tr. 74:1–6.) He has treated approximately one thousand patients with the prior art minocycline. (Tr. 76:13–15.) He has treated approximately ten thousand patients with Minocin and no longer treats patients with the prior art minocycline. (Tr. 78:17–21.) When asked about his

familiarity with intravenous minocycline products on the market, Dr. Friedman testified that he was aware of two: the prior art minocycline, and Minocin. (Tr. 74:7–10.) He stated that he understood that the two were different because Minocin included the addition of magnesium cations. (Tr. 74:11–16.) He testified that Minocin improved the prior art minocycline because it adjusted the pH to be slightly higher, which, in combination with adding magnesium cations, enabled the product to be delivered to the patient at a lower volume. (Tr. 78:2–7.) Dr. Friedman testified that these changes made Minocin a more tolerable and reliable product than the prior art minocycline. (Tr. 78:8–11.)

2. *Dr. Tina deVries*

Plaintiffs’ expert witness Dr. Tina deVries testified as an expert witness regarding all aspects of pharmaceutical research and development, drug formulation, the FDA regulatory approval process for drug products, and the FDA process for making changes to drug product labels, and specifically regarding aqueous pharmaceutical compositions of tetracyclines, including minocycline and doxycycline, in combination with metal cations in preparation as a pharmacist of intravenous formulations. (Tr. 202:6–14.)

Dr. deVries is a pharmaceutical development scientist with over thirty years of experience in pharmaceutical research and development, along with experience in “all aspects of FDA requirements and the drug product approval process” for both generic and patented drugs. (Tr. 192:25–193:6, 196:15–18; PTX-129.) As part of that FDA experience, Dr. deVries has personally and directly communicated with the FDA

regarding drug product labels and approvals. (Tr. 198:21–199:2.) She has specific experience in formulation development, which involves determining how to transform a powder drug into an aqueous product suitable for intravenous administration to patients after combining it with other ingredients. (Tr. 195:12–25.) Dr. deVries has never worked on an intravenous formulation of a tetracycline (such as Minocin), but she maintained that her experience is directly relevant to her testimony in this case because she has worked on products before they are dissolved into a solution suitable for intravenous administration. (Tr. 199:19–200:8.) She has also supervised and observed several projects involving minocycline and a divalent metal cation, including magnesium. (Tr. 200:9–14.)

3. *Mr. David Griffith*

David Griffith, a nonparty witness, is one of the inventors listed on the patents-in-suit. (Tr. 317:1–3.)

Griffith began initial research on Minocin in 2005 while working as the director of nonclinical and clinical sciences at Mpex Pharmaceuticals. (Tr. 318:5–7.) He does not have experience administering tetracyclines, although he does have experience diluting them. (Tr. 381:19–382:3.) He clarified that his research on Minocin was his first interaction with tetracyclines, and he became familiar with the properties of tetracyclines by reading literature. (Tr. 386:2–9.) That research led him to understand that tetracyclines had issues with storage, stability, tolerability, and low pH. (Tr. 391:19–392:14.) Around 2011, Mpex became Rempex Pharmaceuticals, and

Griffith, along with the other inventors, acquired the NDA for Minocin. (Tr. 318:8–13.)

Griffith testified that the '105 Patent and the '802 Patent related to a new formulation of the antibiotic minocycline that sought to improve the low pH, which led to injection site pain and inflammation, and large infusion volumes required by the prior art minocycline. (Tr. 320:7–14, 323:15–324:7.) Griffith stated that he understood that the prior art minocycline had a low pH (between 2.0 and 2.8 for the reconstituted solution) in order to make it more stable. (*Id.* 325:7–20, 326:12–17.) He explained that in order to increase the pH of the prior art minocycline to make it suitable for administration, the solution needed to be diluted in large volumes of diluent in order to avoid venous tolerance issues. (Tr. 328:8–18.) After dilution, the pH would rise to 2.5 to 4, which Griffith testified was still quite low. (Tr. 328:25–329:5.) Griffith testified that administering a solution with such a low pH caused injection site pain, a side effect described on the prior art minocycline's product label. (Tr. 329:6–13.) In addition to the low pH causing injection site problems, the large injection volume was a problem with the prior art minocycline. Griffith explained that the product needed to be administered to patients twice a day every day for ten to fourteen days, which was a very a high volume of intravenous fluid to enter a body and could have a harmful effect on patients who needed other drugs. (Tr. 331:2–18.)

Griffith began working with dimethylamino tetracyclines such as minocycline because it was effective against a particular type of bacteria (*Acinetobacter baumannii*). (Tr. 322:17–323:14.) Griffith and the other inventors began

experimenting with molar ratios of 3:1 (magnesium:minocycline), which caused solubility and stability issues. (Tr. 332:1–9.) They changed their approach and began using a 10:1 molar ratio of magnesium to minocycline, which they found to “surprisingly” lead to more stability. (Tr. 332:13–17.) Along with an increased molar ratio, Griffith and the other inventors unexpectedly found that they could change pH of the formulation and still maintain stability. (Tr. 333:14–16.) In addition, they unexpectedly found that the formulation blocked hemolysis. (Tr. 333:17–334:3.) Because of the higher pH and reduced hemolysis in the newer formulation, the inventors realized that the formulation could be diluted into a lower volume of solution to prepare it for administration. (Tr. 334:4–11.) Griffith testified that each of these benefits is described in the ’802 Patent specification. (Tr. 335:6–21.)

Griffith explained that the specification also lists examples of several tests that the inventors performed, which varied different properties of the Minocin formulation to compare it to the prior art minocycline (Tr. 336:15–19.) One experiment they performed used the same formulation but with doxycycline, a different tetracycline, instead of minocycline, but they found that the same formulation using doxycycline caused solubility issues—the same issues they had expected with minocycline. (Tr. 343:10–344:11.) They performed several in vitro experiments to test hemolysis reduction in the formulation. (Tr. 344:21–351:6.) They discovered that their new formulation, which added divalent cations (such as magnesium) to minocycline at a higher molar ratio resulted in “significant inhibition” of hemolysis and “improve[d]

venous tolerance” compared to the prior art minocycline that did not include divalent cations. (Tr. 350:24–351:10, 360:21–361:6.)

Griffith testified that from 2011 to 2015, he was involved in discussions with the FDA regarding the process of getting FDA approval for the new minocycline formulation. (Tr. 364:22–365:24.) They initially sought a 505(b)(2) mechanism, which would have used previous findings of efficacy and safety of a previously approved minocycline product, but the approach changed when they decided to acquire that product directly. (Tr. 366:3–23.) They filed a supplemental NDA for their new minocycline product, and the previous formulation was removed from the market. (Tr. 367:1–368:4.) The new formulation included an updated label noting the changes in pH level and volume of fluid for administration. (Tr. 368:5–11.) There were some discussions with the FDA about potential human clinical studies for the new formulation, but those studies were not performed because they were not required for approval of the new formulation. (Tr. 372:16–373:12.) He clarified on cross-examination that the FDA would have required clinical trials if Plaintiffs wanted to remove standard information about tetracyclines (such as risk of hemolysis) to show how the new formulation differed from the original formulation, which they decided not to do. (Tr. 382:8–18.) Instead, the FDA’s approval relied on data from the experiments and tests Griffith conducted. (Tr. 373:13–18; *see* PTX-71.) Without the clinical trial, the FDA therefore approved a label including the improved pH and lower infusion volume but without a claim of improved tolerability or reduced injection site hemolysis. (Tr. 384:7–385:25.) The FDA approved the new minocycline

formulation with magnesium at a 5:1 molar ratio to minocycline with a reduced infusion volume of 100 mL to 1,000 mL and a higher pH. (Tr. 380:7–17.)

On cross-examination, Defendant's counsel questioned Griffith about the literature he read before creating the Minocin formulation. Griffith first testified that the patents-in-suit describe the use of a 7-dimethylamino-tetracycline (such as tetracycline, glycylcycline, doxycycline, and minocycline) with a metal cation (such as magnesium, calcium, or iron), but the patents-in-suit specifically focus on minocycline with magnesium. (Tr. 421:9–19, 422:1–10.) Defendant asked Griffith about a 2006 patent that lists minocycline as an active component and identifies magnesium as a preferable metal for complexing. (Tr. 424:13–426:4; DTX-11.) Griffith stated that even though this patent discussed using divalent cations with tetracyclines, the patent used a much lower molar ratio, and Griffith's higher molar ratios had not been tested before. (Tr. 426:8–18.) Griffith explained that it was commonly known information that there were issues with combining metal cations with tetracyclines, and no one had ever tested that formulation as a higher concentration because the assumption was that the formulation would be insoluble and create no new benefits. (Tr. 426:8–24.)

4. *Dr. Alexander Klibanov*

Dr. Alexander Klibanov, Defendant's expert witness, testified as an expert in medicinal chemistry and pharmaceutical formulations. (Tr. 462:12–13.) Dr. Klibanov is a professor of chemistry and bioengineering with expertise in pharmaceutical formulation and medicinal chemistry. (Tr. 459:18–460:3.) Dr. Klibanov has published

hundreds of publications and owns over thirty patents. (Tr. 460:12–21.) He is a consultant for several pharmaceutical companies, member of numerous journal editorial boards, and has received many professional awards for his work. (Tr. 461:1–22.) Dr. Klivanov testified that he has substantial experience in tetracycline formulation, and he has been involved in many projects involving intravenous formulations. (Tr. 464:6–15.) Dr. Klivanov has not, however, treated a patient with minocycline. (Tr. 528:24–529:1.) Nor, according to his testimony, has he been involved in any FDA tetracycline drug approval process. (Tr. 530:5–9.)

5. Dr. Henry Chambers

Defendant's expert witness Dr. Henry Chambers testified as an expert in the field of treatment of infectious diseases and the use of antimicrobial agents, including tetracyclines and minocycline. (Tr. 570:19–579:22.) Dr. Chambers is a physician specializing in infectious diseases. (Tr. 565:9–15.) He has published hundreds of publications in the field of infectious diseases and serves as editor on the Stanford Guide, a manual covering bacterial infections and other infectious diseases. (Tr. 567:1–24.) This manual includes information on minocycline, but Dr. Chambers has never personally prescribed or used intravenous minocycline. (Tr. 568:5–10, 568:25–569:10, 571:12–572:11.)

Dr. Chambers has never had occasion to use intravenous minocycline because it is “almost identical in terms of spectrum” to doxycycline, which is his go-to tetracycline antibiotic. (Tr. 569:3–10.) He explained that doxycycline and minocycline have minor differences on the top of their chemical structure, but are identical on the

bottom of the structure, which is where the antibacterial interaction happens. (Tr. 683:4–14.) When probed about this testimony on cross-examination, he conceded that minocycline and doxycycline do have some differences. Dr. Chambers testified that minocycline is more active than doxycycline against *Acinetobacter baumannii*, the bacteria Minocin treats, as well as other bacteria. (Tr. 630:3–631:23.) He added on cross-examination that he did not have any firsthand experience with whether intravenous minocycline formulations have any injection site tolerability issues such as phlebitis, thrombophlebitis, erythema, pain, or skin necrosis. (Tr. 632:11–633:12.) Nor does he have any firsthand experience reconstituting minocycline or selecting a diluent in order to prepare the formulation for administration to patients. (Tr. 633:13–20.) Dr. Chambers does have experience preparing intravenous formulations for administration to patients, a process that is driven by the instructions on the product label. (Tr. 570:5–18.)

Dr. Chambers has participated in clinical trials involving the use of minocycline, including one with Minocin. (Tr. 573:13–15, 573:16–574:9; PTX-139; PTX-140.) When asked about this clinical trial on cross-examination, Dr. Chambers agreed that minocycline is one of very few antimicrobials that is effective against *Acinetobacter baumannii* and other multidrug-resistant bacteria. (Tr. 637:5–10, 640:17–641:20.) He also agreed that one of the benefits of the Minocin formulation, which was always diluted with 100 mL of normal saline before administering to a test patient, is a lower minimum injection volume of 100 mL. (Tr. 638:1–639:20.)

D. Rounds One and Two: Testimony on Infringement

The bench trial proceeded in four rounds of testimony. Round One consisted of Plaintiffs' evidence on infringement. Round Two consisted of Defendant's testimony on non-infringement and invalidity (obviousness and Section 112 arguments). Round Three consisted of Plaintiffs' response on invalidity and offering secondary considerations. Round Four consisted of Defendant's response to the secondary considerations. This Section discusses both parties' testimony on infringement, which was presented in Rounds One and Two.

1. Dr. Bruce Friedman's Testimony on Infringement

On the issue of infringement, Dr. Friedman concluded, based on his knowledge, experience, and review of the available literature, that "there was induced and contributed-to infringement by [Defendant]." (Tr. 87:16–23.) His conclusion was based on a three-part methodology: (1) determining what elements are required by the asserted patent claims, including the plain and ordinary meaning and a POSA's understanding; (2) determining whether physicians would directly infringe on the claims when using the ANDA product; and (3) determining whether Defendant intends to and will encourage, recommend, or promote a physician to perform the claimed methods, including whether the ANDA product has no other substantial non-infringing use. (Tr. 91:18–92:6.)

When he analyzed whether Defendant indirectly infringed on the patents-in-suit, Dr. Friedman focused on the ANDA product label and how a POSA might interpret that label when administering the product and compared it to Minocin and

the prior art minocycline. (Tr. 93:1–6.) He testified about the ANDA’s common technical document summaries (PTX-021), a document which was provided to the FDA as part of Defendant’s ANDA filings. (Tr. 94:10–16.) He testified that the ANDA product and Minocin were identical to each other and used the same ingredients: same amount of minocycline, same amount of magnesium, and an adjustment of the pH. (Tr. 94:22–95:3.) The ANDA product would therefore have the same benefits of Minocin (reduced delivery volume, stabilized pH, reduced tolerability issues). (Tr. 96:3–13.)

a. Claim 1 of the ’802 Patent

Dr. Friedman testified about each of the claims at issue. He concluded that a physician following the ANDA label would infringe on Claim 1 of the ’802 Patent because the label instructs that it is meant to treat bacterial infections (like Minocin) and explains how to reconstitute and administer the ANDA product. (Tr. 101:9–17.) A POSA would understand that the “composition” discussed in Claim 1 meant the reconstituted solution (which he noted to be different than the diluted solution) because the ’802 Patent specification repeatedly defines the “composition” as such. (Tr. 101:18–103:22.) A POSA would mix that “composition” with a diluent as specified in the label, and then it would be ready for intravenous administration. (Tr. 104:1–5.) A POSA administering the ANDA product would go through that same process. (Tr. 6–10.)

Dr. Friedman also testified that a POSA would understand that the reconstituted solution mentioned in Claim 1 of the ’802 Patent meant a solution

consisting of minocycline, magnesium, a base, and a water-based solvent. (Tr. 106:21–25.) He testified that the ANDA product infringed on this Claim 1 because its label specified the same ingredients: minocycline, magnesium, a base (sodium hydroxide), and a solvent (sterile water). (Tr. 107:2–9.) A physician following the ANDA label would, therefore, meet this element of Claim 1. (Tr. 12–14.)

Dr. Friedman testified that a POSA following the ANDA label would also meet the molar ratio element of Claim 1. Claim 1 states that the molar ratio of magnesium to minocycline is greater than about 4:1. (PTX-001.) Dr. Friedman testified that the ANDA product meets that element because it defines the amount of minocycline and the amount of magnesium in the product, and when a POSA calculates those amounts in terms of molar ratio, it is about a 5:1 ratio, which meets the “greater than about 4:1” element. (Tr. 108:3–11.)

He then testified that a POSA following the ANDA label would meet the pH element of Claim 1. That element states that the composition has a pH “that is no less than 4 and no greater than 6.” (PTX-001.) The ANDA product label would meet that claim element because it states that the pH for the product is between 4.5 and 5. (Tr. 109:1–4.)

Dr. Friedman testified that the ANDA would also meet the injection site hemolysis element of Claim 1. A POSA would understand what injection site hemolysis meant and would understand the benefits of a product that reduced hemolysis. (Tr. 114:4–116:9.) He testified about several properties of a product that affects the rate of hemolysis. First, an “unexpected discovery” revealed that hemolysis

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ANDA label would, therefore, meet the injection site hemolysis element of Claim 1, according to Dr. Friedman. (Tr. 126:9–11.)

On cross-examination on the hemolysis issue, Defendant questioned Dr. Friedman about the lack of clinical trials on hemolysis. Defendant cited a letter from the FDA when Minocin was in the approval process, in which the FDA discussed running clinical trials to support the statement on Minocin's label that the product would reduce hemolysis and tolerability issues as compared to the prior art minocycline. (Tr. 163:9–23; DTX-131.) This discussion was not a recommendation to perform a trial and cited later communications where the FDA stated that a trial was not necessary. (Tr. 163:24–164:11.)

b. Claims 7 and 18 of the '802 Patent

Dr. Friedman next testified that the ANDA product meets Claims 7 and 18 of the '802 Patent, both of which depend from Claim 1. Claim 7 states that the composition has a pH “between about 4.5 to about 5.5,” and the ANDA label specifies that its solution has a pH of 4.5 to 5. (Tr. 126:18–127:10.) Claim 18 states that the total volume of the composition administered is less than 500 mL, which a POSA would understand to mean the diluted solution prepared for administration to a patient. (Tr. 127:22–128:14.) And the ANDA product label states that the product can be administered from 100 to 1000 mLs, but Dr. Friedman testified that this meets Claim 18 because a POSA would always choose to administer the minimum permissible volume. (Tr. 129:9–21.) Accordingly, Dr. Friedman concluded that a physician following the ANDA label would meet Claims 7 and 18 of the '802 Patent.

c. Claims 1 and 27 of the '105 Patent

Claim 27 of the '105 Patent depends from Claim 1, which Dr. Friedman testified to be substantially similar to Claim 1 of the '802 Patent. (Tr. 132:3–13.) Dr. Friedman's conclusions relating to the ingredients (minocycline and magnesium), injection volume, pH level (between 4 and 7), and molar ratio (greater than 3:1) in the '802 Patent apply equally to the '105 Patent. Thus, a physician following the ANDA label would meet those claim elements of Claim 1. (Tr. 132:22–135:17.)

The '105 Patent also includes an element on osmolality, which Dr. Friedman defined as a measure of the weight of particles in a solvent in milliosmols per kilogram, a measurement that can be easily calculated and is often calculated by the pharmacy. (Tr. 135:22–136:3, 138:7–10.) Claim 1 of the '105 Patent defines an osmolality of “less than about 500 mOsmol/kg.” (PTX-002.) The general physiologic standard of care, which is supported by several publications, is to maintain osmolality of less than 500 mOsmol/kg. (Tr. 136:15–137:9; PTX-184; PTX-229.) Dr. Friedman testified that the ANDA product infringes this osmolality element of Claim 1 because the ANDA also inevitably will have an osmolality less than 500 mOsmol/kg to be within the standard of care. (Tr. 140:2–21, 430:8–18.) Even though the ANDA label doesn't expressly mention osmolality, it is still infringing because osmolality can be easily calculated by looking at the ingredients listed on the label. (Tr. 141:10–142:4.) A pharmacist, who typically mixes the drug, is often the one who calculates the osmolality of a formulation before sending it to the patient, but osmolality is nevertheless not a complex calculation. (Tr. 435:7–19.) He concluded that a physician

following the ANDA label would therefore meet the osmolality element of Claim 27. (Tr. 143:23–25.)

2. *Dr. Tina deVries's Testimony on Infringement*

(a) Claims 1, 7, and 18 of the '802 Patent

Dr. deVries testified about the FDA regulatory process for Minocin and any generic drug that copied Minocin. Because Minocin is parenterally (intravenously) administered, it must be a solution to be suitable for administration, and FDA regulations require a copy of an aqueous parenteral drug to have the same active and inactive ingredients in the same amounts as the patented drug. (Tr. 205:24–206:5.) This means, by necessity, that the ANDA product is required to exactly copy Minocin. (Tr. 206:19–21.) Because the copy of the drug is the same as the original, clinical trials are not necessary. (Tr. 206:15–22, 254:5–12.) Dr. deVries testified that these regulatory requirements, in combination with Defendant's literature search when creating the ANDA product, showed that Defendant knew its product would infringe on Plaintiffs' patents. (Tr. 208:20–211:14.)

Dr. deVries compared the Asserted Claims to the ANDA product and label when analyzing whether the ANDA product infringed. Minocin and the ANDA product share the same properties: (1) treat only bacterial infections; (2) administered only intravenously, (3) described as minocycline for injection, (4) ingredients include minocycline, magnesium, and a base; (5) the same amounts of each of those ingredients; (6) a molar ratio of greater than 4:1; and (6) a pH of the reconstituted solution between 4 and 6. (Tr. 212:15–218:15.) The pH stated in Claim

7 of the '802 Patent (between about 4.5 to about 5.5) refers to the pH of the reconstituted solution, not the diluted solution, and Dr. deVries cited a reference to support that opinion. (Tr. 218:11–221:25; 271:11–21; PTX-225.)

Defendant cross-examined Dr. deVries on the volume element of Claim 18. Defendant noted that the Minocin label permits the reconstituted solution to be diluted in up to 1,000 mL of diluent, whereas Claim 18 limits the total volume of the administered composition to be less than 500 mL. (Tr. 274:7–10; PTX-130.) Dr. deVries testified that a physician who administers anywhere between 501 and 1,000 mL as permitted by the label would not meet the elements of Claim 1. (Tr. 274:16–275:7.) But she stressed that no physician would choose to administer that high of a volume to a patient because it would be against the standard of care; rather, any physician would choose to administer the lowest volume permitted by the label, which is 100 mL. (Tr. 274:11–23.) Dr. deVries testified that the ANDA label also specified an administration volume ranging from 100 mL to 1,000 mL, and a physician following this label would also choose to administer the lowest volume possible. (Tr. 275:16–25.)

Dr. deVries then discussed the various studies and experiments on hemolysis that Plaintiffs conducted and submitted to the FDA during the approval process for Minocin. (Tr. 223:11–225:5; PTX-71; PTX-196.) Plaintiffs did not conduct any clinical trials in patients relating to Minocin's improved tolerability claim. (Tr. 252:4–5.) This is because the FDA did not require additional human clinical trials on the hemolysis claim, as the label clearly states the improved pH and improved injection volume. (Tr.

251:3–10.) Clinical trials would have been necessary had Plaintiffs sought to make a change to the clinical claim, something Dr. deVries called “class labeling” that would have the effect of changing the clinical claim for all formulations of all tetracyclines. (Tr. 251:11–19.)

Dr. deVries testified that the inventors conducted some experiments on animals such as mice (because human trials would be harmful), which were still applicable because the experiments studied the same type of blood cells in animals that also appear in humans and would cause the same type of injection site hemolysis. (Tr. 225:6–13.) These studies varied the molar ratio, pH, and other properties and compared the results to a formulation without magnesium to discover whether the formulation with magnesium reduced injection site hemolysis. (Tr. 225:20–226:15.) What they found is that a higher pH and an “unexpected” discovery of a high ratio of magnesium to minocycline were associated with lower injection site hemolysis. (Tr. 284:18–285:5.) Dr. deVries testified that these experiments are well-recognized and reliable models for evaluating injection site hemolysis. (Tr. 227:2–3.) The FDA granted approval to Minocin to completely replace the prior art minocycline because the experiments showed that Minocin reduced the risk of injection site hemolysis as compared to a formulation without magnesium. (Tr. 227:23–228:6.)

Dr. deVries testified that when Defendant submitted its ANDA to the FDA, it explained that its product included magnesium, and that the function of magnesium was hemolysis reduction. (Tr. 230:9–19.) Defendant repeatedly stated that the purpose of magnesium in its ANDA product was to reduce injection site hemolysis.

(Tr. 230:23–231:22; PTX-22; PTX-206; PTX-207; PTX-210; PTX-211.) The FDA then confirmed to Defendant that magnesium in its product was used for hemolysis reduction. (Tr. 231:23–232:8; PTX-220; PTX-19.) Dr. deVries testified that based on this evidence, use of the ANDA product according to its label would meet the elements of Claims 1, 7, and 18 of the '802 Patent. (Tr. 232:16–233:8.)

On cross-examination, Dr. deVries conceded that the ANDA product label does not explicitly state that the product will reduce injection site hemolysis. (Tr. 247:4–14.) But just looking at the information on the label would inform her and any other POSA that hemolysis will be reduced and there will be better tolerability as compared to the prior art minocycline. (*Id.*)

(b) Claims 1 and 27 of the '105 Patent

Dr. deVries's conclusions about the '802 Patent applied equally to the same claim elements and limitations that appear in Claims 1 and 27 of the '105 Patent. (Tr. 233:9–14.)

She then went into the osmolality element of Claim 1, which states an “osmolality less than about 500 mOsmol/kg.” (PTX-002.) Dr. deVries defined osmolality as a property related to the concentration of dissolved molecules or particles in a solution such as an intravenously administered drug. (Tr. 234:1–13.) Osmolality is not mentioned on either Minocin's label or the ANDA product's label, but it is not necessary because osmolality can be calculated based on the amounts of ingredients in the composition that are listed on a product's label. (Tr. 235:22–236:6; 252:14–20.) The osmolality stated in the specification describes the osmolality of the

reconstituted solution, not the admixture, because Claim 1 is describing the reconstituted solution and not the admixture. (Tr. 237:17–239:1.) Accordingly, the osmolality of less than 500 mOsmol/kg listed in the specification is based on the amounts of three ingredients in the composition: magnesium, sodium hydroxide, and 5 mL of water. (Tr. 238:16–25.) When the reconstituted solution is diluted to prepare it for administration to a patient, it should be isotonic, meaning having the same osmolality as blood (around 300 mOsmol/kg). (Tr. 241:3–14, 261:20–21.)

On cross-examination, Dr. deVries was questioned about a manufacturing process development report that Plaintiffs had sent to the FDA when developing Minocin. (DTX-75.) Defendant noted that this report noted the use of 10 mL for reconstitution of the solution in osmolality tests. (Tr. 265:16–21.) Dr. deVries clarified that she understood that a 10 mL vial was used in these tests, rather than 10 mL used in the solution. (*Id.*) She testified that if the results of this experiment were calculated for 5 mL for reconstitution, she approximated that the osmolality would double. (Tr. 307:20–308:5.)

Dr. deVries testified that this same composition was used in the ANDA product and specified on its label, which would necessarily mean that administering the ANDA product according to its label would also result in an osmolality of less than 500 mOsmol/kg. (Tr. 240:14–20.) Dr. deVries testified that in her opinion, the label for the ANDA product would encourage, recommend, and promote physicians to administer the ANDA product intravenously, an act that would meet every Asserted

Claim. (Tr. 244:12–245:6.) Accordingly, she concluded, there will be direct infringement, and Defendant induced that infringement. (Tr. 244:24–245:6.)

3. *Dr. Alexander Klivanov's Testimony on Infringement*

Dr. Klivanov testified of his opinion that Defendant did not infringe on Plaintiffs' product. His opinion is largely based on a disagreement with the meaning of the terms “composition” and “administer” in the patents-in-suit specifications. Dr. Klivanov understands “composition” to be limited to the three listed components (minocycline, magnesium, and a base), so the Minocin label instructing a physician to “administer” the “composition” would mean administering those three ingredients (the reconstituted solution) without a diluent. (Tr. 521:20–522:20.) He testified that the ANDA label, on the other hand, instructs the administration of a diluted solution, not the reconstituted solution. (Tr. 522:25–523:3; DTX-0101.) Dr. Klivanov's opinion is that a POSA administering the ANDA product could not infringe on the claim elements of the '802 Patent because the POSA would follow the instructions on the ANDA product label requiring him to add a diluent—which he testified was not a component of the '802 Patent. (Tr. 524:16–525:10.) Accordingly, Dr. Klivanov testified, there can be no infringement. (Tr. 525:10.)

On cross-examination, Dr. Klivanov testified that he understood there are no differences between the ANDA product and Minocin. (Tr. 549:21–23.) Although he would not concede that Defendant copied Minocin with its ANDA product, Dr. Klivanov did agree that all ingredients and amounts of ingredients between the two

products in their reconstituted forms are identical as required by law. (Tr. 549:24–551:5.)

4. *Dr. Henry Chambers’s Testimony on Infringement*

Dr. Chambers testified that there are three primary differences between the ANDA product label and the Minocin label: (1) description of what is in the vial; (2) how the drug is diluted; and (3) warnings relating to potential side effects of magnesium. (Tr. 581:12–20; DTX-101; DTX-110.) He also compared the old and new Minocin labels, testifying that they are essentially the same except for different volume administration, pH, and diluent volume. (Tr. 583:9–20.) Dr. Chambers’s understanding about the pH level on the label is that it describes the pH of the solution after dilution, because the diluted solution is what is actually administered to the patient. (Tr. 584:2–9.) On cross-examination, he agreed that the Minocin product has an overall improved pH profile compared to the prior art minocycline, which is beneficial because the higher pH profile in Minocin means a lower likelihood of irritation, pain, and toxicity issues. (Tr. 643:17–644:24.) He also testified that there is no relationship between pH levels, volume of administration, and injection site hemolysis, because that relationship is not demonstrated on the label. (Tr. 584:18–22.)

(a) The ’105 Patent

Dr. Chambers testified that the ANDA label does not provide any instructions on osmolality, but a physician would likely ensure that the product is administered at an osmolality “around 500,” a measurement that can be easily calculated by

knowing the osmolality of the other ingredients in the product. (Tr. 585:14–586:21, 634:4–25.) Accordingly, Dr. Chambers’s opinion was that the ANDA label does not infringe because it does not include any information about osmolality on the label, which means it cannot encourage a physician to aim for a particular osmolality. (Tr. 588:2–14.)

(b) The ’802 Patent

For the same reason, Dr. Chambers testified that Defendant did not induce infringement on the injection site hemolysis claim in the ’802 Patent because hemolysis is not mentioned in the Minocin label. (Tr. 590:8–9.) He testified that the label only mentions hemolytic anemia and thrombophlebitis, neither of which are a direct mention of hemolysis. (Tr. 590:9–592:19.) In his opinion, neither phlebitis nor thrombophlebitis (which are mentioned on the Minocin label) are related to hemolysis. (Tr. 597:9–17.) He added that the in vitro tests cited by Plaintiffs in support of the opposing opinion are not sufficient comparators to measuring injection site hemolysis in a patient because those test conditions are very sensitive, so in vitro test results do not apply equally to how a product might affect a human patient. (Tr. 597:20–599:21.) Dr. Chambers was not aware of any agreed-upon definition of the term “injection site hemolysis,” nor any description of its occurrence and how to measure it. (Tr. 596:17–597:8.)

On cross-examination, Dr. Chambers did not recall reviewing statements by Defendant to the FDA that the function of magnesium in its ANDA product was for hemolysis reduction. (Tr. 656:5–20.)

E. Rounds Two, Three, and Four: Testimony on Obviousness

This Section discusses both parties' testimony on the obviousness element of invalidity, which includes both parties' arguments on secondary considerations. This testimony was presented in Rounds Two, Three, and Four.

1. Dr. Alexander Klivanov's Testimony on Obviousness

Dr. Klivanov testified about the basics of intravenous pharmaceutical formulations, including how a solid drug product cannot be administered intravenously but must be dissolved first. (See Tr. 465:1–466:16.) He testified that when developing an intravenous formulation, the formulator would consider stability, solubility, and tolerability of the drug. (Tr. 466:17–468:10.)

He explained that pH and osmolality are important to intravenous administration because the pH and osmolality levels of a formulation should be close to the pH and osmolality levels of blood in order to reduce stress on the patient's body. (Tr. 468:24–470:8.) Dr. Klivanov testified as to the chemical structure of tetracyclines, which is a class of drug compounds that treats bacterial infections. (Tr. 470:14–19.) All tetracyclines share a chemical structure, but minocycline differs from other tetracyclines in specifically the upper portion of the molecule. (Tr. 470:20–22; 474:2–7.) All tetracyclines are able to strongly bind magnesium by forming a complex called a chelate. (Tr. 475:7–16.)

Dr. Klivanov testified about the prior art minocycline and its label. The prior art minocycline label taught that the product was used to treat bacterial infections, and it was a solid powder that needed to be reconstituted in water and then further

diluted to a total volume of 500–1,000 mL to make it suitable for administration. (Tr. 478:10–479:3.) Depending on the type of diluent used, the pH of prior art minocycline varied from 2.0 to 2.8 after reconstitution and 2.5 to 6 after dilution. (Tr. 480:10–481:9.) He testified that a POSA would likely not care about the reconstitution pH and would instead focus on the diluted pH because that is what gets administered into the patient’s body. (Tr. 481:4–9.) Dr. Klibanov testified that there were no significant problems with the prior art minocycline, but if a POSA wanted to improve the formulation, he would review literature on minocycline. (Tr. 482:22.5–11.) Two such references Dr. Klibanov discussed were a Chinese patent application referred to as CN’268 (2008) and a patent application referred to as Gibbs (1989). (Tr. 482:12–16, 489:8–12; DTX-0014; DTX-0012.)

(a) Prior Art Reference CN’268

CN’268 discusses improving doxycycline (a tetracycline that is similar to minocycline) by adding magnesium ions in order to increase pH values and minimize irritability when administered. (Tr. 483:7–25.) CN’268 achieved better solubility, stability, and tolerability by adding magnesium ions to the formulation. (Tr. 484:1–3.) CN’268 increased solubility in the formulation, which then allowed a lower volume in administration. (Tr. 485:21–24.) CN’268 used magnesium ions in higher molar ratios to doxycycline and had a pH value between 3 and 7. (Tr. 486:1–9.)

Dr. Klibanov testified that CN’268 would be relevant to a researcher seeking to improve prior art minocycline because CN’268 studies doxycycline, a close relative of minocycline with structural similarities. (Tr. 486:19–24.) And even though CN’268

is not an intravenous formulation, it would still be relevant from Dr. Klibanov's perspective because CN'268 is also an injectable formulation that happens to be injected into the muscle as opposed to the vein. (Tr. 487:1–12.) CN'268 is also a product designed for veterinary use, which Dr. Klibanov considered to be irrelevant because animals are well-established models for human drug administration. (Tr. 487:16–488:4.) Dr. Klibanov testified that a POSA looking to modify the prior art minocycline would, upon reviewing CN'268, be motivated to add magnesium to a minocycline intravenous formulation to improve stability, solubility, tolerability, and pH. (Tr. 489:1–7.) On cross-examination, Dr. Klibanov confirmed that CN'268 does not mention minocycline, and that he did not discuss on direct examination the function or effects of other ingredients (also called excipients) included in the CN'268 formulation. (Tr. 540:19–541:20.)

(b) Prior Art Reference Gibbs

Dr. Klibanov also testified about a second publication, referred to as the “Gibbs” reference. (DTX-0012.) Gibbs researched adding magnesium ions to minocycline at a molar ratio between 1:1 and 8:1, a formulation that resulted in “improved formulation properties.” (Tr. 489:8–490:14.) The Gibbs formulation used the same ingredients as the prior art minocycline but added magnesium, because magnesium formed chelates with doxycycline and minocycline, causing beneficial effects (such as improved solubility and stability and reduced toxicity and irritability). (Tr. 491:16–492:13, 500:14–23.) Dr. Klibanov explained that doxycycline and minocycline were listed together in the Gibbs reference more than two dozen

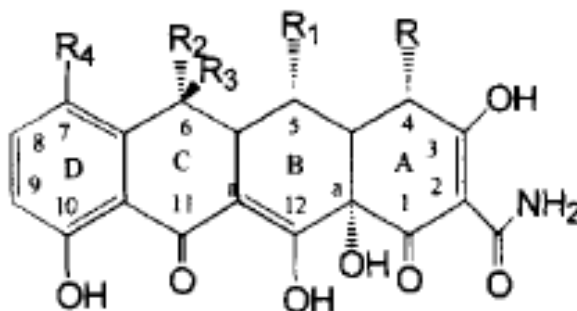
times, which a POSA would understand to mean that doxycycline and minocycline are essentially interchangeable in terms of their interaction with magnesium. (Tr. 491:21–492:4.) When read in relation to CN’268, Dr. Klibanov testified that Gibbs reinforced the idea that what CN’268 revealed about doxycycline’s relationship with magnesium also applies to minocycline. (Tr. 492:5–13.) But on cross-examination, Dr. Klibanov conceded that Gibbs does not expressly disclose any data on minocycline formulations but instead focuses on doxycycline formulations. (Tr. 541:25–542:12.) Dr. Klibanov maintained, however, that the doxycycline examples specified in Gibbs provide procedures for making minocycline formulations, and a POSA could follow the procedure specified for doxycycline but use minocycline instead. (Tr. 544:22–547:2.)

(c) Additional Prior Art References

In addition to CN’268 and Gibbs, Dr. Klibanov pointed out four other prior art references that taught a molar ratio of 3:1 to 8:1 of magnesium ions to a tetracycline. (Tr. 494:6–15; DTX-0008; DTX-0009; DTX-0006; DTX-0007.) Of these four references, none is specific to minocycline, but Dr. Klibanov argued that a POSA seeking to make a minocycline formulation would not ignore these references because of minocycline’s similarity to other tetracyclines. (Tr. 495:3–12.) None of these references explicitly disclose intravenous formulations, but they disclose parenteral formulations, which encompass intravenous formulations. (Tr. 548:9–20.)

(d) Chemical Similarities Among Tetracyclines

Dr. Klibanov testified that there are “profound structural similarities” among all tetracyclines, particularly with respect to the structure of the lower portion of the tetracycline ring. (Tr. 495:11–21.) Magnesium complexation to tetracyclines has been extensively studied, and it is well known that magnesium binds with all tetracyclines in the lower portion of the B and C tetracycline rings as shown in the figure below—the portion of a tetracycline molecule that does not change across all tetracyclines. (Tr. 495:13–496:15, 479:11–18; DTX-0174.)



On cross-examination, Plaintiffs asked Dr. Klibanov about previous statements he had made about how seemingly small structural differences between two molecules can result in large differences in the properties of the substance, a statement Dr. Klibanov agreed remained true today. (Tr. 531:13–532:20.) Dr. Klibanov then agreed with Plaintiffs that there are three structural differences between minocycline and doxycycline. (Tr. 532:23–533:1.)

(e) Ultimate Opinions on Obviousness of the '802 Patent

Based on an understanding of the chemical structure of minocycline and a familiarity with CN'268 and Gibbs, Dr. Klibanov testified that a POSA should

reasonably expect to successfully create a minocycline formulation with magnesium that improved stability, solubility, and hemolysis. (Tr. 500:24–501:6.) He testified that a POSA following the prior art minocycline’s label would have diluted the reconstituted solution to bring the volume to 500–1,000 mL and obtain a final pH of 4.5 to 6, but that same POSA who was familiar with CN’268 and Gibbs would have been motivated to add magnesium at a ratio of up to 8:1 to that prior art minocycline formulation because they would have an understanding that magnesium would improve solubility and enable a lower dosage. (Tr. 501:12–502:9.)

Regarding Claim 1 of the ’802 Patent, Dr. Klivanov testified that the prior art minocycline covers all claim elements except the addition of magnesium, but a POSA familiar with CN’268 and Gibbs would have been motivated to add magnesium to the prior art minocycline. (Tr. 504:16–22.) He also testified that the term “injection site hemolysis” in Claim 1 is vague because there is no agreed-upon teaching for how to measure it, but a POSA would nevertheless reasonably expect hemolysis to be reduced in a formulation that included magnesium. (Tr. 505:1–15.) This is because hemolysis reduction is a necessary and “inherent” result of administering a formulation with magnesium and minocycline. (Tr. 505:20–506:10.) Dr. Klivanov also testified that Gibbs taught a magnesium to minocycline molar ratio of up to 8:1, which overlaps with the claimed range of 4:1 in Claim 1. (Tr. 508:3–9.) He also stated that the pH claim limitation in Claim 1 (a pH between 4 and 6) overlaps with the pH in the prior art minocycline when diluted (4.5–6), and the pH levels in the prior art (3–7 in CN’268 and 5–7 in Gibbs). (Tr. 508:18–23.) Dr. Klivanov thus concluded that the

Claim 1 elements about magnesium, reduced hemolysis, a higher molar ratio, and a higher pH level were obvious. (Tr. 507:14–508:2.)

Regarding Claim 7 of the '802 Patent, which narrows the pH range to between 4.5 and 5.5, Dr. Klibanov testified that the prior art references (the prior art minocycline label, CN'268, and Gibbs) teach a pH range that overlaps and encompasses the range in Claim 7. (Tr. 510:1–11.)

Regarding Claim 18 of the '802 Patent, which limits the total administered volume of the composition to 500 mL, Dr. Klibanov testified that Gibbs specifically taught a low injection volume of 5 mL, and the prior art minocycline label also allowed a volume of 500 mL. (Tr. 510:19–511:6.) Based on this prior art, Dr. Klibanov testified that a POSA would have understood that an administration volume of less than 500 mL would have been obvious. (Tr. 511:9–12.)

Dr. Klibanov's ultimate opinion regarding the Asserted Claims of the '802 Patent, based on the prior art references (the prior art minocycline label, CN'268, and Gibbs), was that the Asserted Claims would have been obvious to a POSA. (Tr. 511:13–18.)

(d) Ultimate Opinions on Obviousness of the '105 Patent

Dr. Klibanov first testified that all the opinions he had about the '802 Patent claim elements applied equally to the same claim elements in the '105 Patent. (Tr. 512:4–8, 513:15–515:13.)

Dr. Klibanov also testified about the osmolality element of Claim 1 of the '105 Patent, which teaches an osmolality of less than 500 mOsmol/kg. (*See* PTX-002.) He

testified that the prior art references do not explicitly discuss osmolality, but a POSA would know that the osmolality of the formulation must be near the 300 mOsmol/kg osmolality level of blood, which is within the claimed range of 500 mOsmol/kg. (Tr. 512:17–24, 515:16–21; *see also* DTX-0175.) He stated that the osmolality level of the formulation is “unequivocally dictate[d]” by and an “inevitable result of” the ingredients and concentrations within the formulation. (Tr. 512:25–513:4.)

Dr. Klibanov’s ultimate opinion regarding obviousness of the Asserted Claims in the ’105 Patent was that all Asserted Claims would have been obvious to a POSA, based on prior art references including the prior art minocycline label, CN’268, and Gibbs. (Tr. 516:10–18.)

2. *Dr. Richard Chambers’s Testimony on Obviousness*

Dr. Chambers testified that he agreed with Dr. Klibanov’s assessment of obviousness. (Tr. 618:6–11.) He did not rely on any references other than Gibbs and CN’268 in making this conclusion. (Tr. 676:25–677:7.)

(a) Prior Art Reference Gibbs

Dr. Chambers first testified that a physician reviewing Gibbs, which focuses on doxycycline, would apply conclusions and research about doxycycline to minocycline because the two tetracyclines have similar chemical structures and identical magnesium binding. (Tr. 618:14–22.) Gibbs, which studies an intramuscular formulation, describes the use of oil in its formulation, but Dr. Chambers argued that a POSA would disregard that oil use for an intravenous formulation because injecting oil into a patient’s bloodstream would be dangerous. (Tr. 619:1–621:3.) But that same

POSA would still find the remaining information in Gibbs to be helpful because it includes information about how magnesium interacts with doxycycline and, by extension, with minocycline. (Tr. 620:19–622:13.)

When asked about this inclusion of oil on cross-examination, Dr. Chambers testified that oil acts as a “surfactant” in the Gibbs formulation, which increases the solubility of doxycycline. (Tr. 662:2–15.) Gibbs requires an antioxidant to be added to the doxycycline formulation in order to stabilize it. (Tr. 16–19.)

(b) Prior Art Reference CN’268

Dr. Chambers testified about the toxicity and tissue irritability disclosures mentioned in the CN’268 publication. (See PTX-14.) CN’268, like Gibbs, studies an intramuscular formulation, and is directed to veterinary use. But he maintained that CN’268 is still relevant to intravenous formulations because high toxicity and irritability at the site of an intramuscular injection would translate to lower toxicity and irritability at the site of an intravenous injection. (Tr. 624:12–23.) He also testified on cross-examination that CN’268 only concerns formulations of doxycycline injection for veterinary use and does not mention minocycline anywhere. (Tr. 666:5–19.)

He also testified that CN’268 describes that magnesium improves a doxycycline formulation by increasing its solubility, improving the pH, and reducing toxicity and tissue irritability. (Tr. 624:5–9.) But all claims in the CN’268 publication require the use of a dissolvent and an antioxidant. (Tr. 670:12–22.) Dr. Chambers then discussed an experiment described in CN’268, which was conducted via

intramuscular administration in pigs, that resulted in no toxicity and other side effects. (Tr. 625:2–5.) But he conceded that CN'268 does not explicitly and directly mention or disclose hemolysis. (Tr. 671:10–12.)

Dr. Chambers concluded that a POSA would be motivated to combine the prior art minocycline, Gibbs, and CN'268 to achieve the claimed formulation and would have a reasonable expectation that developing such an improved formulation would be successful. (Tr. 625:6–22.)

3. *Dr. Bruce Friedman's Testimony on Obviousness*

(a) Prior Art References

Dr. Friedman repeated his testimony about the issues he witnessed with prior art minocycline. He testified that the problems included injection site tolerability issues, improper pH, and large minimum injection volumes. (Tr. 696:1–3.) As to injection tolerability issues, he explained that a POSA would understand that injection site hemolysis is a risk for any patient that is triggered when injected, and it can create signs and symptoms such as thrombophlebitis, phlebitis, erythema, pain, and potentially skin damage. (Tr. 696:5–25.) As to improper pH, he explained that a lower pH (such as 2–2.8 in prior art minocycline) is more likely to induce injection site hemolysis, a fact he said was supported by two publications: the 2002 Jan-Peter paper and the 1982 Jones paper. (Tr. 697:25–699:7; PTX-179; PTX-181.) As to injection volumes, Dr. Friedman testified that a higher volume of fluid administered to a patient (such as a minimum 500 mLs in prior art minocycline) means increased cell contact and, therefore, increased risk of intolerability. (Tr. 699:8–700:1.)

Dr. Friedman cited several publications to support his opinion that there were known issues with the prior art minocycline. First, a 1995 Klein paper includes research on only doxycycline because all other parenteral tetracyclines (such as minocycline) were associated with thrombophlebitis and hepatic toxicity (liver damage). (Tr. 700:2–23; PTX-182.) Klein teaches that using minocycline carries many risks, and a physician administering it to a patient with a bacterial infection needs to be careful. (Tr. 701:24–702:9.) Second, Dr. Friedman cited a 1996 Sweetana paper. (See PTX-233.) Sweetana measures pH from the reconstituted solution, and the prior art minocycline had one of the lowest pHs of several other formulations studied in the Sweetana paper. (Tr. 702:11–17, 703:9.) Dr. Friedman did not cite to any article that showed reduced hemolysis of Minocin as compared to the prior art minocycline. (Tr. 753:4–7.) Nor did he discuss the Gibbs reference or the CN'268 reference. (Tr. 762:20–763:4.)

(b) Secondary Considerations

Dr. Friedman also relied on his own experience to support his opinion. At the burn and wound center where he is employed, he saw many patients who were treated with prior art minocycline and had hemolysis symptom such as skin breakage and damage, which would then extend the length of their stay. (Tr. 704:5–14.) But he continued to use prior art minocycline because they had few other options to treat a bacterial infection. (Tr. 704:25–705:7.) Dr. Friedman testified that minocycline was especially effective against bacterial infections as opposed to other tetracyclines such as doxycycline because of the addition of nitrogen on the second methyl ring, which

changes the minocycline's chemical structure to afford it unique features such as a lower likelihood of resistance patterns. (Tr. 706:11–25.) Because of this difference, Dr. Friedman testified, a POSA would not extrapolate disclosures and findings about doxycycline and apply them to minocycline. (Tr. 707:1–10.)

Based on this testimony, Dr. Friedman concluded that there was a long-felt but unmet need for an improved intravenous formulation of minocycline that reduced injection site tolerability issues. (Tr. 708:18–709:3.) He testified that there were “valiant efforts” to improve prior art minocycline, but no one was successful. (Tr. 709:17–19.) A POSA could not try to increase the pH of the prior art minocycline because it would lead to solubility issues, nor could a POSA decrease the minimum injection volume because lower pH required higher injection volumes to avoid tolerability issues. (Tr. 709:21–710:7; PTX-175.)

Dr. Friedman testified that the Minocin product was a “much-needed breakthrough.” (Tr. 711:13–14.) Minocin added magnesium at a 5:1 molar ratio, and had a lower pH and injection volume than prior art minocycline. (Tr. 711:1–8.) Minocin was effective against several bacteria that other antibiotics could not treat, and it reduced the risk of injection site hemolysis, allowing it to be routinely used to treat patients. (Tr. 711:11–23.)

On cross-examination, Dr. Friedman was questioned about the pH element of the minocycline formulations. Both the prior art minocycline and Minocin's product labels require dilution before the formulation is administered using diluents such as Lactated Ringer's or a normal saline. Lactated Ringer's is an option to use as a diluent

but not the standard of care, and normal saline was the recommended standard of care. (Tr. 722:5–724:24.) This is because Lactated Ringer’s is a formulation used primarily to restore fluids to patients low on volume due to trauma or burns, not a diluent for pharmaceuticals. (Tr. 765:18–766:2.) If Lactated Ringer’s was used as a diluent in an administration of the prior art minocycline (although it would be highly unlikely for a POSA to use that diluent), the pH of the diluted solution would be 4.5 to 6.0. (Tr. 728:3–729:7.)

4. *Dr. Tina deVries Testimony on Obviousness*

(a) Response to Defendant’s Obviousness Arguments

Dr. deVries testified about the Gibbs and CN’268 references that Dr. Chambers and Dr. Klibanov discussed. First, Gibbs was considered by the patent examiner during prosecution of the patents-in-suit. (Tr. 809:21–24; PTX-132.) Gibbs does not disclose any examples of minocycline, nor any attempts to make a minocycline formulation; instead, Gibbs only studies doxycycline. (Tr. 809:6–810:8.) The Gibbs compositions were administered intramuscularly without any examples of intravenous administration. (Tr. 810:20–25.) Dr. deVries explained that a POSA would not extrapolate this data and apply it to intravenous minocycline formulations. First, a POSA would want to see additional data on minocycline specifically, especially in the context of the prior art references she previously testified about. (Tr. 810:9–15.) Second, a POSA could not extrapolate findings about intramuscular formulations to intravenous formulations because intravenous formulations must be administered as a solution to avoid precipitation, whereas an intramuscular injection

does not have to be a solution and can accommodate another phase such as an oil to help solubilize the formulation. (Tr. 811:3–812:2.) Gibbs also teaches an antioxidant was necessary to stabilize doxycycline, without any discussion or implication that magnesium could improve stability or solubility. (*Id.* 812:18–24.) But Gibbs does explain that an antioxidant is optional if a POSA wants to ensure stability. (Tr. 896:2–12.) Although Gibbs discusses an 8:1 ratio of magnesium to drug, it does not discuss the significance of the molar ratio of metal cations. (Tr. 812:25–813:2, 845:25–846:4.) Accordingly, Dr. deVries testified that a POSA would not have considered the Gibbs reference to be relevant. (Tr. 813:6–8.)

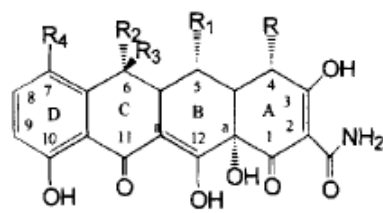
The CN'268 reference studies an intramuscular doxycycline injection for veterinary use. (Tr. 813:13–814:2.) CN'268 does not disclose anything about either minocycline or intravenous formulations. (Tr. 813:13–14, 814:3–5.) Like Gibbs, CN'268 taught that an antioxidant is necessary to stabilize doxycycline, rather than magnesium. (Tr. 814:25–815:7.) Nor does CN'268 discuss the significance of a higher molar ratio. (Tr. 815:8–10.) CN'268 does discuss magnesium. (Tr. 845:19–21.) Dr. deVries agreed that CN'268 was not considered by the patent office during the Minocin approval process. (Tr. 846:5–10.)

Dr. deVries testified about the other prior art references Dr. Klibanov discussed (Weidenheimer, 1967; Beutel, 1972; Akazawa, 1974; Noseworthy, 1976). She explained that none of those references mentioned minocycline at all, all taught the addition of other excipients to stabilize the formulation, and all studied intramuscular formulations. (Tr. 815:14–816:5.) She testified that a POSA seeking to

make a minocycline solution for intravenous administration would not have learned anything from these references. (Tr. 816:10–13.)

(b) Chemical Structures of Minocycline and Doxycycline

Dr. deVries testified that doxycycline is not a 7-dimethylamino-tetracycline, which the claims of the patents-in-suit are directed to. (Tr. 821:7–16.) Doxycycline and minocycline have three structural differences in the upper group of the molecule, as indicated in R₁, R₂, and R₄ of Rows D and E in the below figures from the 1998 Nelson reference:

	Tetracycline Natural Products					
	R	R ₁	R ₂	R ₃	R ₄	
A. Chlortetracycline	N(CH ₃) ₂	H	CH ₃	H	Cl	
B. Oxytetracycline	N(CH ₃) ₂	OH	CH ₃	OH	H	
C. Tetracycline	N(CH ₃) ₂	H	CH ₃	H	H	
Tetracycline Semi-synthetic Compounds						
D. Minocycline	N(CH ₃) ₂	H	H	H	N(CH ₃) ₂	
E. Doxycycline	N(CH ₃) ₂	OH	CH ₃	H	H	
F. Methacycline	N(CH ₃) ₂	OH	= CH ₂	-	H	

(Tr. 821:22–822:5; PTX-151.) Although it is true that magnesium only binds to the lower region of the tetracycline structure, the Nelson reference says other studies show that the upper group is also implicated. (Tr. 822:6–15.) The Nelson reference also teaches that modification of the upper group may “drastically alter” chemical attributes of a tetracycline, which can lead to changes in solubility. (Tr. 823:2–7.) Accordingly, Dr. deVries explained, a POSA would understand that the three structural differences between minocycline and doxycycline in the upper region could significantly affect how the molecules interact with metal cations. (Tr. 823:22–824:1.)

Dr. deVries also testified that the 1974 Barringer reference teaches that the differences between minocycline and doxycycline, including solubility, are attributed

specifically to the presence of a 7-dimethylamino group in minocycline that does not appear in doxycycline. (Tr. 824:6–19; PTX-152.)

Based on these references, Dr. deVries concluded that a POSA would not have been motivated to attempt minocycline formulations based on prior art references that only disclose information on doxycycline. (Tr. 825:1–4.) A POSA attempting such a strategy would not have had a reasonable expectation of success. (Tr. 825:5–8.)

(c) Secondary Consideration #1: Teaching Away

Dr. deVries testified on objective teaching away in prior art references. She began by testifying about her own 2006 publication. (PTX-134.) Her experiments involved an aqueous solution of minocycline with metal cations (such as magnesium) and an increased pH, which resulted in immediate formation of insoluble particles (which she described as “suspension”). (Tr. 775:4–19.) The molar ratio of metal cations to minocycline used in her experiments ranged from 1:3 to 3:1. (Tr. 775:20–23.) Thus, she testified that her experiments taught that a molar ratio up to 3:1 became insoluble when a base was added, at which point the formulation was at a pH level near 4. (Tr. 776:4–7, 782:12–18.) That a higher molar ratio of magnesium to minocycline did not result in solubility issues was therefore surprising to Dr. deVries, especially in combination with other literature warning about the combination of metal cations with minocycline. (Tr. 776:24–777:15.)

Dr. deVries testified about this other literature. First, a 1998 Yalkowsky paper explains how hemolysis and phlebitis are major adverse effects of intravenous administration. (Tr. 780:15–781:1.) Next, a 1974 Barringer paper that studies the

solubility of minocycline at a 2:1 molar ratio of magnesium ions resulted in a seven-fold reduction in solubility in the presence of magnesium at a pH of 6.5. (Tr. 782:23–783:20; PTX-152.) Dr. deVries testified that a POSA reading Barringer would learn that calcium or magnesium should not be included in a minocycline formulation because it would react with minocycline and precipitate¹³ out of solution. (Tr. 783:21–784:1.) She testified that this information is applicable to intravenous solutions, which must be solutions for administration, so the potential for precipitation and insolubility is important. (Tr. 788:7–14.) With this understanding, she testified that the inventors of the patents-in-suit surprisingly found that adding magnesium into a minocycline formulation at a 5:1 ratio was able to result in a solution suitable for intravenous administration. (Tr. 788:15–789:4.)

Third, a 1983 Berthon reference studied the interaction between magnesium and minocycline. (Tr. 789:5–11; PTX-158.) This reference found the presence of precipitation in fluids that combined magnesium and minocycline at a higher pH. (Tr. 789:17–790:3.) She stated that a POSA would have learned from Berthon to avoid combining magnesium with minocycline for an intravenous solution. (Tr. 790:4–8.) Fourth, a 1976 Allen reference conveyed the same message. (Tr. 790:20–23.) The Allen reference surveyed the treatment and use of minocycline in a clinic, concluding that minocycline chelates with metal cations with a loss of solubility. (Tr. 790:12–19; PTX-157.)

¹³ “Precipitation” is a process by which a substance is “separated from a solution by the action of a reagent so that a precipitate forms. *Precipitation*, Taber’s Medical Dictionary Online (24th ed.).

Fifth, a 1982 Pawelczyk reference considered by the FDA investigates the stability of minocycline in aqueous solutions within a broad pH range. (Tr. 791:9–22; PTX-133.) DeVries testified that Pawelczyk taught that the degradation of minocycline increased at a pH of 4 to 6, meaning that a POSA reading Pawelczyk would learn to keep the pH of a minocycline formulation between 2 and 3 to maintain stability. (Tr. 793:4–20.) Pawelczyk also studies the effect of metal ions on the degradation rate of minocycline, which showed that the addition of magnesium did not have any distinct effect on the rate of degradation versus a formulation without magnesium. (Tr. 794:3–13.) Pawelczyk was pre-formulation work reporting data on experiments, not attempting to create a pharmaceutical formulation. (Tr. 850:25–851:7.)

In summary, Dr. deVries testified that these five references would teach a POSA away from the claimed invention in the patents-in-suit. (Tr. 795:1–3.) This is because the reference taught a POSA to avoid formulating solutions of minocycline over a pH of 4, avoid adding metal cations, and avoid adding high molar ratios of metal cations to minocycline. (Tr. 4–11.)

(d) Secondary Consideration #2: Length of Intervening Time

Dr. deVries testified that the length of intervening time between the prior art minocycline (1973) and the patents-in-suit (2010) is evidence of non-obviousness. (Tr. 799:8–13.) She cited several publications to support her opinion that no one could determine how to fix the prior art minocycline for almost forty years. (Tr. 14–16.) Dr. deVries testified in particular about the pH of the prior art minocycline, which is 2 to

2.8 for the reconstituted solution and 2.5 to 4 for the diluted solution. (Tr. 796:19–797:2.) The Broadhead article teaches an avoidance of a pH less than 3, which may cause pain and phlebitis. (Tr. 796:3–15; PTX-225.) A 1998 Kokotis article found that an acidic drug with a pH below 4.1 could damage a vein’s inner layer. (Tr. 797:7–17; PTX-185.) The 2002 Jan-Peter article stated that the risk of hemolysis, precipitation, phlebitis, and pain is well-known to be higher at a lower pH level. (Tr. 797:21–798:4; PTX-179.) Dr. deVries testified that a POSA would be aware of all these publications and, in view of that, would know that the pH of the prior art minocycline was so low to maintain solubility and stability. (Tr. 798:11–22.) No changes were made to the prior art minocycline formulation until Minocin was approved forty years later because no one knew how to improve it. (Tr. 799:8–16.)

On cross-examination, Dr. deVries was asked about the Broadhead reference. She testified that Broadhead stated a parenteral product should have a pH close to physiological range (approximately 7.4) unless precluded by solubility or stability problems, but a wide pH range can be tolerated when administered intravenously. (Tr. 852:19–853:15.) Broadhead also taught that hypertonic solutions (osmolality above 500) were preferable to hypotonic solutions (a lower osmolality) because of a risk of hemolysis associated with hypotonic solutions. (Tr. 854:23–855:15.) Dr. deVries did not agree that Broadhead was thus teaching that increased osmolality reduced hemolysis. (Tr. 855:3–7.) Dr. DeVries also did not agree that hypotonic formulations are included in the ’105 Patent. (Tr. 857:19–21.)

(e) Secondary Consideration #3: Unexpected Results

Dr. deVries disagreed with Defendant's argument that CN'268 and Gibbs were the closest prior art and should have been used as comparators. (Tr. 800:25–801:3.) Both references were void of any data about minocycline formulations, did not concern intravenous formulations, and taught the addition of stabilizers and solubilizers. (Tr. 801:4–9.) Dr. deVries testified that the inventors of the patents-in-suit had “unexpected and surprising results.” (Tr. 801:16.) They “found that by adding high molar ratios of magnesium cations greater than 3 to 1, they were able to successfully create an aqueous solution of minocycline . . . suitable for intravenous administration” with a composition and administration pH over 4 for all diluents. (Tr. 801:17–24.) And this formulation did not have significant solubility or stability issues, was able to be administered at a volume less than 500 mLs, and reduced injection site hemolysis. (Tr. 801:17–802:2.) Dr. deVries testified that she was surprised by these results because they were the exact opposite of her findings in the 2006 publication. (Tr. 802:3–17.)

Dr. deVries stated that the FDA reviewed all experimental data generated by the inventors. (Tr. 802:13–15.) The FDA concluded that those experiments showed that the addition of magnesium to minocycline improved stability and solubility at higher pH values, had the potential to reduce injection site hemolysis compared to the prior art minocycline, and enabled administration at a smaller volume. (Tr. 804:8–22.) The FDA thus was saying that the studies and data showed that the new formulation improved the prior art minocycline. (Tr. 806:6–14.)

In summary, Dr. deVries affirmed that the results of the inventors' experiments showed that compositions that meet the limitations of the Asserted Claims are sufficiently stable and soluble for intravenous administration and reduce the risk of injection site hemolysis relative to compositions that do not include magnesium. (Tr. 807:7–17.) She testified that the unexpected results were due to the claimed features of the invention, including a molar ratio of magnesium to minocycline of greater than 3:1. (Tr. 807:18–22.) Dr. deVries concluded that there is a nexus between the unexpected results and the claimed invention, which is objective evidence of non-obviousness. (Tr. 807:23–808:3.)

Dr. deVries concluded that a POSA would not have been motivated to combine these prior art references with the prior art minocycline because they did not discuss minocycline, intravenous formulations, or molar ratios, and they discussed the presence of additional solubilizing agents not in the Asserted Claims. (Tr. 817:11–25.) She added that even if a POSA was so motivated, the POSA could not have had a reasonable expectation of success in achieving the claimed invention. (Tr. 818:17–21.)

5. *Round Four: Defendant's Response on Secondary Considerations*

(a) Dr. Klibanov's Response

In Round Four of argument, Dr. Klibanov testified in response to Plaintiffs' secondary considerations arguments. First, he responded to Dr. deVries's teaching away arguments. He explained that in order to teach away, a reference must criticize, discredit, or otherwise discourage a POSA from making a claim, which he testified

Dr. deVries had not done for the pH, magnesium, or molar ratio claims. (Tr. 911:16–912:12.) Dr. Klibanov also discussed Dr. deVries’s testimony about the Barringer article. He disagreed that it teaches away from intravenous formulations with high concentrations of metal cations, because the article concerns oral absorption, not aqueous solutions or intravenous formulations. (Tr. 912:13–915:1.) Accordingly, he testified, Barringer would not have taught a POSA away from creating an aqueous solution of minocycline with a high molar ratio of magnesium at a pH above 4. (Tr. 916:5–22.) But on cross-examination, he agreed that Barringer did teach that the minocycline and magnesium complex can precipitate from an aqueous solution depending on the pH value, becoming unsuitable for intravenous administration. (Tr. 920:20–921:23.) Dr. Klibanov also disagreed with Dr. deVries that a POSA would have expected such a formulation to have stability and solubility issues based on the prior art. (Tr. 916:23–917:5.)

Dr. Klibanov’s ultimate opinions on obviousness were: (1) there were no surprising and unexpected results; (2) no references taught away from the claimed invention; (3) there was no long-felt need met by the formulation; and (4) copying did not suggest the claims were innovative. (Tr. 917:6–19.)

(b) Dr. Chambers’s Response

In round four of argument, Dr. Chambers testified that Minocin did not change the use, efficacy, and safety of the prior art minocycline. (Tr. 908:14–21.) Both formulations treated the *Acinetobacter* bacteria, and the prior art minocycline could have continued to have been used to treat that bacteria if it had not been removed

This Section discusses both parties' testimony on the Section 112 arguments of invalidity, including lack of enablement and lack of written description. This testimony was presented in Rounds Two, Three, and Four.

Dr. Klibanov testified as to his invalidity opinion regarding lack of enablement and lack of written description of the patents-in-suit. This opinion applied only to the pH claims asserted: (1) Claim 1 of the '802 Patent requiring a pH between 4 and 6, and (2) Claim 1 of the '105 Patent requiring a pH between 4 and 7. (Tr. 525:18–526:1.) Dr. Klibanov testified that based on the disclosures in the patents-in-suit, a POSA would not be able to make formulations suitable for intravenous administration at the pH levels claimed. (Tr. 527:11–14.) This is because under some conditions that would fall within the scope of the claims, minocycline would be insoluble and thus unsuitable for administration to a patient. (Tr. 526:12–527:14.)

Dr. Chambers testified that the '802 Patent specification suffers from lack of written description and enablement because it does not define, measure, or report injection site hemolysis, and therefore does not teach a POSA how to reduce it. (Tr. 600:9–17.)

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3. *Dr. Bruce Friedman's Testimony on Section 112*

Dr. Friedman testified in response to Defendant's claim of lack of written description and lack of enablement as to the administration volume in the '802 Patent and osmolality in the '105 Patent and the injection site hemolysis claims.

Dr. Friedman first testified that the total volume of the administered composition in the '802 Patent was 500 mL, and this referred to the diluted solution. (Tr. 713:18–23.) But a POSA would know that some embodiments of the formulation could be formulated with much lower volumes and could adjust the formulation accordingly. (Tr. 713:25–714:13.) A POSA would never administer such a low formulation as to make the drug toxic or no longer therapeutically effective. (Tr. 714:14–18.) It is true that the '802 Patent does not specify a lower limit of volume, but a POSA would know how much to decrease the volume of a formulation to avoid toxicity. (Tr. 746:20–747:2.) Even though the '802 Patent does not have any examples of tests conducted at less than 50 mL of volume, a POSA would not have to conduct experiments to determine how low of a volume would be appropriate because they would know based on their experience. (Tr. 746:10–748:17.) Dr. Friedman also testified on cross-examination that there were several articles submitted to the FDA on the use of minocycline (without magnesium) at a volume between 100 mL and 500 mL. (*Id.* 754:2–759:5.) Ultimately, Dr. Friedman testified that he believed the '802 Patent was enabled and supported by adequate written description. (Tr. 715:4–5.)

Dr. Friedman then testified that the injection site hemolysis claims were not indefinite because a POSA would know what injection site hemolysis is, how it's

As to hemolysis, Dr. deVries testified that a POSA would understand, after reviewing the hemolysis data in the specifications, that a formulation within the scope of the Asserted Claims would reduce hemolysis. (Tr. 835:1–5.) A POSA would not be concerned that the hemolysis experiments in the specifications were conducted in vitro versus on human patients. (Tr. 835:14–18.) The FDA knew that the inventors used in vitro tests as a model for hemolysis. (Tr. 836:7–11.) Specifically, Dr. deVries stated that the inventors’ use of rabbit blood cells in the experiment was a good thing because those cells are very sensitive, so any improvement or benefit that can be seen in rabbit ear blood cells will mean that the inventors can reliably assume that the same benefit will be seen in other cells. (Tr. 836:23–637:13.) On cross-examination,

Defendant examined Dr. deVries about these rabbit blood cell tests. (*See* Tr. 864:11–872:8.) Defendant questioned the results of three in vitro tests that the inventors conducted and Plaintiffs relied on, even though these tests only showed “minor differences.” (Tr. 869:4–16.) Dr. deVries did not agree with how Defendant construed this experiment. (Tr. 869:17–18.)

V. CONCLUSIONS OF LAW

In patent infringement cases, the patentee bears the burden of proving infringement of every claim by a preponderance of the evidence. *Creative Compounds, LLC v. Starmark Lab’s*, 651 F.3d 1303, 1314 (Fed. Cir. 2011) (quoting *SRI Int’l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1123 (Fed. Cir. 1985)). If the patentee does not meet that burden, “the patentee loses regardless of whether the accused comes forward with any evidence to the contrary.” *Id.*

An accused infringer can respond by asserting affirmative defenses: (1) non-infringement; (2) invalidity of the patent on any ground specified as a condition for patentability (e.g., obviousness or lack of novelty); or (3) invalidity of the patent or any claim in suit for failure to comply with any requirement of § 112 (e.g., indefiniteness, lack of enablement, or lack of written description). 35 U.S.C. § 282(b). A patent is presumed valid, but a defendant asserting an invalidity defense may rebut that presumption by proving invalidity by a heightened standard of clear and convincing evidence. *Id.* § 282(a); *Microsoft Corp. v. i4i Ltd. P’ship*, 564 U.S. 91, 97 (2011). Then, in response to an invalidity for obviousness defense, the plaintiff can rebut by presenting secondary considerations establishing objective evidence of non-

obviousness by a preponderance of the evidence. *See Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016). Secondary considerations of non-obviousness can include (1) commercial success, (2) copying, (3) long-felt but unmet need, (4) skepticism or disbelief, (5) positive recognition, and (6) unexpected results. *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). But evidence of secondary considerations does not always overcome a strong showing of obviousness. *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008).

Plaintiffs allege that Defendant has infringed on Claims 1, 7, and 18 of the '802 Patent and Claim 27 of the '105 Patent. Defendant argues that it has not infringed and, even if it had infringed, the patents-in-suit are invalid for obviousness, indefiniteness, lack of enablement, and lack of written description. Plaintiffs respond by presenting several secondary considerations to argue non-obviousness. The Court's analysis of each argument follows.

A. Infringement

1. Direct Infringement

Plaintiffs argue that Defendant's marketing and use of its ANDA product will indirectly infringe the patents-in-suit. But to prevail on an indirect infringement claim, a plaintiff must first prove direct infringement by a third party. *See Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 341 (1961); *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 920–21 (2014). A party directly infringes when it “without authority makes, uses, offers to sell, or sells any patented invention, within the United States” 35 U.S.C. § 271(a). To determine

infringement, the court must compare the “asserted claim as properly construed” to the “accused method or product.” *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1581–82 (Fed. Cir. 1996); *see also Mas-Hamilton Grp. v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998). To prevail on direct infringement claims, the plaintiff must show infringement of every claim limitation by a preponderance of the evidence. *See, e.g., Bayer AG v. Elan Pharm. Rsch. Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000).

To prove direct infringement, Plaintiffs must show that “if [Defendant’s ANDA product] were put on the market, it would infringe the [patents-in-suit].” *Genentech, Inc. v. Sandoz Inc.*, 55 F.4th 1368, 1379 (Fed. Cir. 2022) (quoting *Vanda Pharms. Inc. v. W.-Ward Pharms. Int’l Ltd.*, 887 F.3d 1117, 1129 (Fed. Cir. 2018)). This determination requires “‘consideration of all the relevant evidence,’ including the proposed label’s instructions and physician practice.” *Id.* (quoting *Ferring B.V. v. Watson Lab’s, Inc.-Fla.*, 764 F.3d 1401, 1408 (Fed. Cir. 2014)). Courts may also consider the ANDA product itself, any materials the generic drug company submitted to the FDA, and “other pertinent evidence provided by the parties.” *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1570 (Fed. Cir. 1997). In short, courts are permitted to—and regularly do—consider relevant evidence outside the ANDA product’s label to evaluate whether the product directly infringes the claims. *See Genentech*, 55 F.4th at 1379–80; *Ferring B.V.*, 764 F.3d at 1409–10; *Par Pharm., Inc. v. Eagle Pharms., Inc.*, 44 F.4th 1379, 1383–84 (Fed. Cir. 2022) (“If the ANDA specification does not speak clearly and directly to the question of infringement, courts may look to other relevant evidence . . . to assess whether a proposed product will infringe.”).

Plaintiffs argue that Defendant is liable for indirect infringement because a physician using the generic ANDA product would directly infringe on the patents-in-suit. They contend that because the allegedly infringing generic product's label instructs a physician on how to use the product, that physician's act of following the ANDA product label would meet the claim elements at issue in this case, thus directly infringing on the patents-in-suit. (Dkt. 252 ¶¶ 102, 151; Dkt. 253 ¶ 30.) Defendant argues that Plaintiffs have failed to prove that the ANDA product directly infringes on the osmolality element of the '105 Patent and the injection site hemolysis element of the '802 Patent. (Dkt. 250 at 21–27; Dkt. 254 at 11–15; Dkt. 255 ¶¶ 46–48.)

(a) A Physician Using Defendant's ANDA Product Will Directly Infringe on Claim 27 of the '105 Patent.

Claim 27 of the '105 Patent depends on Claim 1, which specifies that administering Minocin according to the specified instructions will cause an osmolality of less than 500 mOsmol/kg. (PTX-002.) Neither the Minocin label nor the ANDA label explicitly mentions osmolality. Plaintiffs argue that even though neither label explicitly mentions osmolality, a physician following the ANDA label nevertheless infringes because the product will inevitably have an osmolality of less than 500 mOsmol/kg due to its chemical composition. (Dkt. 252 ¶¶ 135–38.) Plaintiffs cite “numerous direct measurements of osmolality” of the ANDA product that they performed, all of which resulted in an osmolality of less than 500 mOsmol/kg; thus, Plaintiff argues, the ANDA product is within the scope of the '105 Patent's osmolality claim. (*Id.* ¶ 139.) Defendant counters that Plaintiffs' experiments used a different composition volume (10 mL) than what was specified in the ANDA (5 mL), so the test

results cannot show infringement of the osmolality limitation. (Dkt. 255 ¶¶ 43–44.) But Plaintiffs insist that they did rely on experimental data using 5 mL of composition. (Dkt. 251 at 11.)

Osmolality is a property of a composition, meaning it is measured through simple calculations based on the ingredients in a composition. *See Osmolality*, Taber’s Medical Dictionary Online (24th ed.). Accordingly, a POSA looking at the amounts of ingredients in a product described on its label would be able to discern the osmolality of the solution. (Dkt. 252 ¶ 138; Tr. 235:22–236:20, 651:18–21.) The parties agree on the following three facts: (1) osmolality is a property of the composition that can be calculated by looking at the ingredients on the label; (2) the osmolality standard of care is a level below 500 mOsmol/kg; and (3) the Minocin and ANDA product labels are identical and use identical ingredients at identical amounts, as required by the FDA.

Thus, a physician following the ANDA label will perform the same exact process as a physician following the Minocin label. There is no evidence that a physician using Defendant’s ANDA product will deviate from the standard of care; accordingly, a physician administering either product will ensure that the osmolality level is less than 500 mOsmol/kg. Just as administering Minocin will inevitably lead to an osmolality of less than 500 mOsmol/kg, administering the ANDA product will also inevitably lead to an osmolality of less than 500 mOsmol/kg. Defendant does not dispute this.

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(b) A Physician Using Defendant's ANDA Product Will Directly Infringe on Claims 1, 7, and 18 of the '802 Patent.

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(Dkt. 250 at 26; Dkt. 254 at 12–13.) Defendant contends that an experiment conducted on non-human subjects cannot prove that hemolysis will be reduced in Plaintiffs’ product designed for human use, much less prove that Defendant’s ANDA product will reduce hemolysis in human subjects. (Dkt. 250 at 26.) Defendant also argues that Plaintiffs’ tests did not truly show reduced injection site hemolysis relative to a composition that does not include magnesium. (*Id.* at 26–27.) And Defendant finds fault in Dr. Friedman’s “say-so” testimony about his experience and observations of hemolysis in his patients because Dr. Friedman did not corroborate that testimony with any documentation. (*Id.* at 27; Dkt. 254 at 12–13.)

But, as with the osmolality element of the ’105 Patent, injection site hemolysis reduction is a property of both Minocin and the ANDA label. It is not a specific step that a physician who administers either product must do before injecting it into a patient; instead, hemolysis reduction is a beneficial property that all patients who receive the products will experience. As with osmolality, that the ANDA product is meant to reduce hemolysis is not explicitly stated on the product label. But what is clear from the label is that it has a higher pH and a lower injection volume. A POSA reading that label would understand that if an intravenous formulation has a pH that is too low, it would cause irritation, pain, and other tolerability issues to the patient. As such, a POSA would immediately know that a high pH and low injection volume would mean reduced hemolysis for the patient in comparison to the prior art minocycline with its lower pH and higher injection volume. This alone means that a

physician following Defendant's ANDA instructions would directly infringe on the injection hemolysis element of Claim 1 of the '802 Patent.

As to Defendant's argument about the lack of comparator human trials, such trials would be cost prohibitive and would inappropriately put patients at harm because prior art minocycline had known issues. (Dkt. 249 at 21.) Nor did the FDA require such trials. The FDA approved Minocin as an improvement over the prior art minocycline based on the existing data presented by the inventors showing an improvement in hemolysis reduction as compared to the prior art minocycline. The FDA only required clinical human trials if Plaintiffs were seeking to change the side effect warnings on the label—information called “class labeling” that appears on all formulations of all tetracyclines. Because Plaintiffs did not set out to do this, human clinical trials were not necessary.

Plaintiffs instead appropriately relied on substantial experimental data from in vitro and in vivo studies directly measuring the incidence of injection site hemolysis. These studies showed that the composition in the '802 Patent reduces the risk of injection site hemolysis in comparison to a formulation with magnesium. (*See* PTX-1; PTX-087; PTX-196.) All experiments tested aqueous solutions with minocycline and magnesium at varying molar ratios and pH levels against the prior art minocycline formulation. The experiments were conducted on mice and human endothelial cells (not injected directly into human veins), but that does not make the experiments less useful. Conducting this type of experiment on humans would have come with a higher risk of harm to any volunteer receiving the prior art minocycline,

which had known tolerability issues. And, as several experts testified, the models used in these experiments are well-known to be reliable methods to evaluate injection site hemolysis in humans because the models study the same cell types that would be damaged in human injection site hemolysis. Because these experiments showed reduced injection site hemolysis in the claimed invention versus the prior art minocycline, it was appropriate for Plaintiffs and the FDA to rely on them. These experiments provide adequate support for the injection site hemolysis reduction element of Claim 1.

Dr. Friedman, who has extensive experience administering intravenous minocycline to patients to treat bacterial infections, also testified that he no longer uses the prior art minocycline because Minocin significantly reduces tolerability issues. Both of Defendant's expert witnesses, Dr. Klibanov and Dr. Chambers, admitted that they do not have any experience administering minocycline to patients intravenously. Dr. Friedman's real-world experience thus weighs heavily in support of Plaintiffs' argument that its product reduces the incidence of hemolysis.

Based on this evidence, the Court holds that a POSA administering the ANDA product would infringe on the injection site hemolysis element of Claim 1 of the '802 Patent. Plaintiffs can justify its injection site hemolysis reduction claim with the experiments it conducted and Dr. Friedman's testimony. And at bottom, the ANDA label, even though it does not explicitly mention hemolysis, will inevitably lead physicians to directly infringe on the hemolysis reduction claim.

2. Defendant is Liable for Induced Infringement.

Induced infringement occurs when an alleged infringer actively induces direct infringement by another party. 35 U.S.C. § 271(b) (“Whoever actively induces infringement of a patent shall be liable as an infringer.”). The patent holder must establish “first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another’s infringement.” *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1304–05 (Fed. Cir. 2002). But, in pharmaceutical cases, the “mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient” for induced infringement. *Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015.) A plaintiff must prove specific intent, knowledge, and action to induce infringement. *Id.* (citing *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003)).

The “knowledge” element of induced infringement requires “knowledge of the existence of the patent that is infringed” and “knowledge that the induced acts constitute patent infringement.” *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 765 (2011); *see also Commil USA, LLC v. Cisco Sys., Inc.*, 575 U.S. 632, 639 (2015). An alleged infringer possesses the requisite intent to induce infringement when there is “[e]vidence of active steps taken to encourage infringement, such as advertising an infringing use or instructing how to engage in an infringing use.” *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 915 (2005). These actions show “an affirmative intent that the product be used to infringe,” thus constituting induced infringement. *Id.*

In pharmaceutical patent cases, the label or instructions on an ANDA can be evidence of an intent to induce infringement. Evidence that the ANDA’s labeling or instructions “would inevitably lead some physicians to infringe” would “establish[] the requisite intent for inducement.” *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017). *See also Sanofi v. Watson Lab’s Inc.*, 875 F.3d 636, 644–45 (Fed. Cir. 2017) (“inferred intent” to induce infringement present because defendant’s proposed labels encouraged physicians to prescribe the medication, knowing that such a prescription would be infringement); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (“The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [defendant’s] affirmative intent to induce infringement.”); *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009) (“The question is not, however, whether a user following the instruments may end up using the device in an infringing way. Rather it is whether [the defendant’s] instructions teach an infringing use of the device such that we are willing to infer from those instructions an affirmative intent to infringe the patent.”).

Defendant argues that it did not induce infringement of the osmolality and hemolysis elements in the patents-in-suit because the ANDA product label mentions neither. (Dkt. 250 at 22–25, 27–30; Dkt. 254 at 16–22.) Accordingly, Defendant argues, it cannot possibly encourage or instruct a POSA to infringe on those claim elements. (*Id.*) But, as stated earlier, the Court’s infringement analysis does not begin and end with the product label. Infringement of claim elements can occur when the

ANDA label encourages the claimed administration of the product, even when what is claimed is not explicitly stated on the ANDA label. And because both osmolality of less than 500 mOsmol/kg and reduced injection site hemolysis are properties of the patents-in-suits' composition that inevitably result from the proper administration of the composition, a POSA following the identical ANDA label will also inevitably administer a formulation with osmolality less than 500 mOsmol/kg and reduced injection site hemolysis. Accordingly, because Defendant's label will encourage and instruct a POSA to administer the ANDA product in a way that infringes the patents-in-suit, the Court infers Defendant's knowledge and affirmative intent to infringe the patents-in-suit.

In addition, as to the hemolysis reduction claim element of the '802 Patent, Plaintiffs presented evidence of Defendant's knowledge that its ANDA product would infringe when Defendant submitted its ANDA to the FDA. Defendant, in its submission, explicitly stated at multiple times that the function of magnesium in its product was to reduce injection site hemolysis. Dr. deVries testified to this, and Defendant did not dispute it. Defendant's affirmative statements to the FDA that its ANDA product would reduce injection site hemolysis is additional evidence that Defendant had knowledge that its product would infringe. Accordingly, the Court finds that Defendant induced infringement of the disputed claim elements.

3. *Defendant Is Liable for Contributory Infringement.*

Contributory infringement occurs when the alleged infringer sells a material component of a patented invention for practicing a patented process, and the material

component has no substantial noninfringing use. 35 U.S.C. § 271(c) (“Whoever . . . sells within the United States . . . component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial non-infringing use, shall be liable as a contributory infringer.”). Therefore, a contributory infringement action succeeds if four elements are proven: (1) there is direct infringement; (2) the accused infringer had knowledge of the patent; (3) the component had no substantial non-infringing use; and (4) the component is a material part of the invention. *Fujitsu Ltd. V. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010).

The “knowledge” element requires that the alleged infringer have had knowledge both that the component was patented, and that the use of it would be infringing. *Commil*, 575 U.S. at 639; *Fujitsu*, 620 F.3d at 1330. Whether a use is considered “substantial” is often the key inquiry. A component has no “substantial” non-infringing use if it is not “unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental.” *Vita-Mix Corp.*, 581 F.3d at 1327. A court considers “not only the use’s frequency, but also the use’s practicability, the invention’s intended purpose, and the intended market” in assessing whether an asserted non-infringing use was “substantial.” *i4i Ltd. P’ship v. Microsoft Corp.*, 598 F.3d 831, 851 (Fed. Cir. 2010).

Defendant argues it is not liable for contributory infringement because it did not have knowledge of infringement, and because Plaintiffs cannot prove direct infringement. (Dkt. 250 at 22–23, 27–28.) But Plaintiffs have proven direct infringement, and the Court has found that Defendant had the requisite knowledge of infringement. There is no dispute as to the fourth element of contributory infringement, regarding whether the ANDA product is a material part of the invention, because the ANDA product is identical to the invention in the patents-in-suit.

Defendant argues that as to the third element of contributory infringement, Plaintiff failed to show no “substantial” non-infringing use because some of the injection volumes and pH levels allowed by the ANDA label are outside of the claim elements. (*Id.* at 18–19.) But those injection volumes and pH levels would be, as Dr. deVries and Dr. Friedman testified, outside the standard of care for any POSA administering the product. It would be highly unusual, unsafe, and unlikely for a POSA to administer the ANDA product outside of the measurements within the claim elements. Accordingly, the injection volumes and pH levels that fall outside the claim elements are not “substantial” for purposes of contributory infringement. The purpose for which the ANDA product is to be used is to treat bacterial infections, and a POSA following the ANDA label to treat bacterial infections will administer the ANDA product in a way that meets all of the disputed claim elements. In other words, there is no substantial non-infringing use for the ANDA product. Defendant is also liable for contributory infringement.

B. Invalidity—Obviousness

A patent is invalid for obviousness when the nature of the differences between the claimed invention and the prior art would have rendered the subject matter of the invention obvious to a POSA. 35 U.S.C. § 103 (“A patent for a claimed invention may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.”). The party seeking to invalidate a patent based on obviousness “must demonstrate ‘by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.’ ” *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)).

Defendant argues that Minocin was an obvious invention because a POSA would have been motivated to combine three prior art references (the prior art minocycline product, CN’268, and Gibbs) to achieve the claimed invention with a reasonable likelihood of success. (Dkt. 250; Dkt. 254.) Plaintiffs argue that Defendant has not met its burden to show obviousness by clear and convincing evidence, and they present several secondary considerations of non-obviousness. (Dkts. 249; 251.)

1. *A POSA Would Not Have Been Motivated to Combine the Prior Art Minocycline, CN'268, and Gibbs to Achieve the Claimed Invention with a Reasonable Likelihood of Success.*

A court may find a motivation to combine prior art references by looking to (1) teachings in prior art, (2) the common sense of a POSA, or (3) any need or problem known to a POSA that would be addressed by the claimed invention. *Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1354 (Fed. Cir. 2013). But when analyzing a motivation to combine, a court must be careful to not base motivation on hindsight or reading the invention's teachings into the prior art. *See, e.g., Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 36 (1966) (Courts must "resist the temptation to read into the prior art the teachings of the invention in issue."); *Grain Processing Corp. v. Am. Maize-Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) (quoting *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983)) ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'").

A "reasonable expectation of success" does not require an absolute expectation of success, just that the prior art have at least provided some indication of "which parameters are critical" and "which of many possible choices is likely to be successful." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). In summary, when there is a "design need or market pressure to solve a problem" and "a finite number of identified, predictable solutions," a POSA has reason to pursue known options to solve that problem. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007). If pursuing those options "leads to

the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense” and therefore is obvious. *Id.*

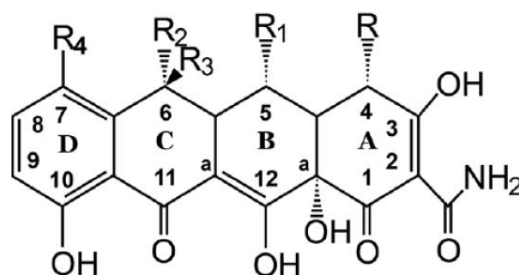
The extent of Defendant’s obviousness argument hangs on three prior art references: the prior art minocycline, CN’268, and Gibbs. Defendant argues that these three prior art references would have motivated a POSA to improve the prior art minocycline by adding magnesium at a higher molar ratio to minocycline and would have reasonably expected to be successful in doing so. Defendant first argues that the prior art minocycline product taught that minocycline treated bacterial infections caused by the *Acinetobacter* bacteria using a formulation of minocycline reconstituted in 5 mL of water and then further diluted in 500–1,000 mL of a diluent. Defendant then argues that CN’268 taught that the addition of magnesium to a parenteral doxycycline formulation would improve solubility, stability, and tolerability, and this teaching could be extended to minocycline. Finally, Defendant argues that Gibbs taught that adding magnesium to tetracyclines at a molar ratio of up to 8:1 would improve a formulation. Defendant contends that these prior art references are very similar to the claims at issue in this case because they generally taught that the addition of magnesium to tetracyclines could improve the pH, and because doxycycline and minocycline can be used interchangeably because they have similar chemical structures.

But there are significant differences between these three prior art references and Minocin that Defendant fails properly to account for. As to the first prior art reference, it is true that the prior art minocycline teaches a minocycline formulation

to treat bacterial infections. But the prior art minocycline teaches a formulation with a much lower reconstituted pH of 2.0 to 2.8. Minocin teaches a minocycline formulation that adds magnesium to achieve a higher reconstituted pH. Defendant argues that the prior art minocycline does teach a higher pH covered by the patents-in-suit when the prior art minocycline is diluted with Lactated Ringer's. This argument is of no matter because the Court has defined the pH levels in the patents-in-suit to refer to the reconstituted solution, not the diluted solution. But even if the Court did agree with Defendant's proposed construction, the higher pH of Lactated Ringer's stated in the prior art minocycline label is still not covered by the claims at issue because, as Dr. Friedman testified, that diluent is not within the standard of care for intravenous administrations and would be considered inappropriate for intravenous use by a POSA.

As to the other two prior art references Defendant cites, CN'268 and Gibbs, a POSA would not have been motivated to combine them with the prior art minocycline product to achieve the claimed invention. CN'268 and Gibbs contain several important differences from Minocin. First, both concern doxycycline formulations, not minocycline formulations. Second, both disclose only intramuscular formulations, not intravenous formulations. Third, both teach the addition of a surfactant, dissolvent, or antioxidant to improve solubility and stability. Fourth, neither mention hemolysis or the significance of an increased molar ratio of magnesium to minocycline. The Court will address each of these differences in turn.

First, the Court cannot agree with Defendant that a POSA would be motivated to extrapolate findings in CN'268 and Gibbs about doxycycline to minocycline. Even though the two tetracyclines share structural similarities, there are sufficient differences between the two. The parties agree that minocycline and doxycycline share a chemical structure made up of four fused rings as shown in the figure below.



The parties also agree that minocycline and doxycycline differ in the upper rings (notated by the letter R) but have the same bottom rings. They agree that magnesium binds to the lower rings. Defendant uses this similarity to argue that because magnesium binds to the lower rings in both doxycycline and minocycline, a POSA could extrapolate findings about a magnesium-doxycycline formulation to a magnesium-minocycline formulation.

But it is not that simple. Defendant relies on the Nelson reference to support its argument that magnesium binds with doxycycline and minocycline at the exact same location. But Defendant fails to mention that Nelson also teaches that the upper region of the two tetracyclines is also implicated when binding with a metal cation like magnesium. When the upper regions are different, as they are in doxycycline and minocycline, the two compounds can act in dramatically different ways when they interact with magnesium. Dr. deVries testified to this fact, and Dr. Klivanov also

agreed that small structural differences in two similar compounds can nevertheless lead to significant differences in how the compounds interact with metal cations.

In addition, Dr. Friedman, the only witness who had any experience administering and treating patients with minocycline, testified credibly that minocycline was specifically effective against the *Acinetobacter* bacteria. Defendant also agreed that minocycline was more effective than doxycycline against this particular bacteria, which Minocin is intended to treat.

Defendant also argues that the Gibbs reference confirms the relevance of doxycycline formulations to minocycline formulations because Gibbs represents that the two can be used interchangeably. But, as Dr. deVries testified, and Defendant does not dispute, Gibbs does not provide any data on minocycline formulations. The entirety of Gibbs discusses and provides examples and experiments on doxycycline formulations, not minocycline formulations.

Second, both CN'268 and Gibbs disclose intramuscular formulations, not intravenous formulations. Defendant argues that findings on intramuscular formulations can be extrapolated to intravenous formulation because the only difference between the two is the injection site: a muscle versus a vein. But, as Dr. deVries testified, there are more differences than just the injection site. Importantly, an intramuscular formulation can be injected into the muscle without being a fully aqueous solution. But an intravenous formulation cannot be injected into the vein unless it is fully solubilized, meaning all components must be dissolved. Full solubility is, therefore, extremely important for an intravenous formulation such as

what is described in the patents-in-suit. Accordingly, two intramuscular formulations studied by CN'268 and Gibbs would not have been helpful to a POSA because they do not necessarily require complete solubility.

Relatedly, to improve solubility in the CN'268 and Gibbs intramuscular formulations, both discuss the addition of a solubilizing agent such as oil to improve the solubility of both formulations. But the patents-in-suit do not allow for the addition of a solubilizing agent. And to improve stability, CN'268 and Gibbs discuss the addition of a stabilizing agent. Neither discusses that magnesium would have any effect, much less a positive effect, on stability and solubility in the doxycycline formulations that they studied. A POSA would thus understand that CN'268 and Gibbs teach that adding solubilizing and stabilizing agents are necessary to improve stability and solubility for doxycycline formulations. They would not, as Defendant argues, learn from these prior art references that magnesium could improve solubility and stability in a minocycline formulation.

Finally, neither CN'268 nor Gibbs discusses anything about reduced injection site hemolysis or the significance of a high molar ratio of magnesium to minocycline. Defendant points out that Gibbs teaches a formulation in molar ratios up to 8:1, which overlaps with the claimed 4:1 range. But, as Plaintiffs counter, Gibbs does not teach anything about the significance of a higher molar ratio, thus not teaching a POSA to create a formulation with a higher magnesium-minocycline ratio. And CN'268 teaches nothing about a higher molar ratio; instead, it teaches the opposite ratio than the molar ratio that is claimed. CN'268 teaches an excess of doxycycline to

magnesium—the opposite of the claimed excess of magnesium to minocycline. Thus, neither CN’268 nor Gibbs would motivate a POSA to combine magnesium with the prior art minocycline at a high molar ratio of magnesium to minocycline.

Defendant makes brief references to a handful of additional prior art references to support their arguments. But these references suffer from the same faults as CN’268 and Gibbs—they only study doxycycline, they discuss intramuscular formulations, and they require the addition of stabilizing and solubilizing agents.

Accordingly, for these reasons, Defendant has not shown by clear and convincing evidence that a POSA would have been motivated to combine the prior art minocycline, CN’268, and Gibbs to create the claimed invention. Even if a POSA was so motivated, the POSA would not have a reasonable expectation of success. First, doxycycline and minocycline are similar compounds with similar structures, but they have important differences, especially in how they respond to magnesium binding. Second, CN’268 and Gibbs teach very different formulations than the claimed invention. A POSA would not be motivated to extrapolate findings about doxycycline-based intramuscular formulations to a minocycline-based intravenous formulation. The claims at issue are thus not obvious.

2. Secondary Considerations

Plaintiffs’ evidence of secondary considerations support this Court’s finding that the Asserted Claims are not obvious. A party attempting to refute an assertion of obviousness may present objective evidence of non-obviousness (also referred to as “secondary considerations”) such as (1) commercial success, (2) long-felt but unmet

The initial secondary consideration Plaintiffs offer is that prior art taught away from the claimed invention. Prior art “may be said to teach away when a person of ordinary skill, upon reading the [prior art], would be discouraged from following the path set out . . . or would be led in a direction divergent from the path that was taken by the applicant.” *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

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First, the deVries 2006 reference teaches away from the claimed invention in the patents-in-suit. The deVries 2006 reference studied a formulation of minocycline and magnesium at a molar ratio of up to 3:1 with an increased pH. DeVries's experiments consistently resulted in minocycline precipitating out of solution and becoming insoluble, making it unsuitable and dangerous for intravenous administration. This reference taught away from the claimed invention because it would teach a POSA that any minocycline-magnesium formulation formulated with a molar ratio of greater than 3:1 would be expected to be insoluble. Defendant argues in its post-trial briefing (neither expert testified about deVries 2006) that deVries 2006 was irrelevant to a POSA because it studies oral formulations. True enough, but those oral formulations were aqueous solutions, making them more suitable for comparison to the claimed invention, which is also an aqueous solution. Thus, deVries 2006 still teaches a POSA to not mix magnesium and minocycline at a molar ratio higher than 3:1 if the POSA wants to create a safe aqueous solution.

Second, the Barringer 1974 reference teaches away from the claimed invention for the same reason deVries 2006 does—magnesium-minocycline formulations become insoluble at a molar ratio higher than 2:1. Dr. Klibanov testified that Barringer was irrelevant to a POSA because it discussed oral absorption. But Dr. Klibanov also testified that Barringer relevantly taught that adding magnesium to minocycline in aqueous solutions causes insolubility and precipitation, which is relevant to whether such a solution would be suitable for intravenous administration.

Third, the Berthon 1983 and Allen 1967 references teach away from the claimed invention because they teach that the solubility of minocycline decreases when mixed with magnesium and an increased pH. These references would teach a POSA to avoid mixing magnesium with minocycline at a higher pH because it would not lead to a suitable soluble intravenous formulation.

Fourth, the Pawelczyk 1982 reference teaches away from the claimed invention because it teaches that minocycline is more stable at a lower pH and begins to degrade at a pH around 4. Pawelczyk also teaches that the addition of magnesium does nothing to improve stability of minocycline in aqueous solutions in comparison to aqueous minocycline solutions without magnesium. Accordingly, the Pawelczyk reference teaches a POSA that a minocycline formulation with a higher pH would be unstable, and the addition of magnesium would not do anything to improve stability.

These prior art references thus teach away from the claimed invention. They teach that a magnesium-minocycline formulation at a higher molar ratio and a higher pH level would not result in a stable and soluble formulation. But the patents-in-suit found the opposite—a magnesium-minocycline formulation at a molar ratio of greater than 4:1 would result in a soluble and stable formulation at a higher pH.

(b) Plaintiffs Presented Evidence of Unexpected Results.

Evidence of unexpected results includes evidence that the new invention contains a combination of known elements that resulted in superior and unexpected properties as compared to the prior art. *See, e.g., Procter & Gamble Co.*, 566 F.3d at 997–98. Unexpected results are also important to a showing of non-obviousness

because the fact that the results were unexpected means that a POSA would not have had a reasonable expectation of success. *See Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1309 (Fed. Cir. 2010).

The prior art references discussed above taught an avoidance of adding magnesium to minocycline at a molar ratio of 3:1 because it would lead to solubility and stability problems. But the inventors of the patents-in-suit found that a molar ratio of greater than 3:1 could successfully create an aqueous solution suitable for intravenous administration at a higher pH and a lower volume of administration. These were unexpected results in the light of the prior art which taught away from these results, and these unexpected results were a clear improvement over the prior art minocycline.

(c) The Claimed Invention Met a Long-Felt But Unmet Need.

Evidence of a long-felt but unmet need that was met by the new invention is important to a showing of non-obviousness because it shows that if there was a need for a solution to a problem for a long time that took a long time to resolve, the eventual resolution was likely not obvious. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006).

The prior art minocycline was first published in 1973 and never substantively changed until Minocin was approved in 2015. A POSA knew that the prior art minocycline had solubility and stability problems requiring it to be administered at a lower pH and a higher injection volume. A POSA also knew that low pH levels caused irritability and injection site hemolysis. These issues made the prior art

minocycline highly unfavored for use in treating bacterial infections, as Dr. Friedman testified. Attempts to improve the solution were unsuccessful and ran into similar solubility and stability problems.

Minocin successfully solved these solubility and stability problems because of the addition of magnesium at a higher molar ratio. This addition enabled the formulation to be administered a higher and more tolerable pH level and a lower injection volume, which led to reduced tolerability and injection site hemolysis issues. Dr. Friedman, who has treated numerous patients with Minocin and no longer uses the prior art minocycline at all, testified that Minocin resolved all the solubility and stability issues that came with the prior art minocycline. Defendant's experts, who have never administered minocycline, disagreed at first but later agreed that the addition of magnesium in Minocin improves solubility and stability.

Thus, the prior art minocycline's shortcomings presented a need for improvement, a need that was unmet for over forty years until Minocin entered the market.

(d) Plaintiffs Presented Evidence that Defendant Copied Minocin, But Copying Is Required in Hatch-Waxman Litigation.

Evidence that the alleged infringer copied the invention can be a secondary consideration of non-obviousness, because a presumption exists that a POSA would have tried to obtain the same results as the invention but without copying. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1336 (Fed. Cir. 2016). In Hatch-Waxman pharmaceutical cases, however, evidence of copying is often not probative because "a showing of bioequivalence is required for FDA approval" in those cases. *Bayer*

Healthcare Pharms., Inc. v. Watson Pharms., Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013).

Plaintiffs argue that because Defendant chose to copy the Minocin product instead of the prior art minocycline product, this choice shows that Defendant knew the Minocin product had some benefit over the prior art minocycline. This choice thus points to non-obviousness, according to Plaintiffs. It may be true that Defendant chose to copy Minocin over the prior art minocycline because Defendant believed that Minocin had benefits that the prior art minocycline did not have. But such copying is less persuasive evidence of non-obviousness in Hatch-Waxman litigation, because the FDA requires that an ANDA product be the exact same as the patented product, so copying is necessary.

C. Section 112 Invalidity Defenses

Defendant asserts that indefiniteness, lack of written description, and lack of written enablement render the patents-in-suit invalid. Section 112 requires patent specifications to distinctly define the subject matter of the patent, contain a written description of the invention, and contain an explanation on the manner and process of using the invention. 35 U.S.C. § 112. Failure of a patent to satisfy these requirements may render the patent invalid. *See Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010).

1. Indefiniteness

An inventor must distinctly claim the subject matter of the invention in the patent claims. 35 U.S.C. § 112(b) (“The specification shall conclude with one or more

claims particularly pointing out and distinctly claiming the subject matter which the inventor . . . regards as the invention.”). A patent that fails to do so may be invalid for indefiniteness. Specifically, a patent is “invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

Defendant argues that Claims 1, 7, and 18 of the ’802 Patent are invalid for indefiniteness because each claim requires that injection site hemolysis be reduced as compared to a formulation without magnesium, but the ’802 Patent does not define injection site hemolysis or instruct how to measure it. Because, according to Defendant, the claim term creates a “zone of uncertainty,” the ’802 Patent claims are invalid for indefiniteness. (Dkt. 250 at 56.)

Defendant’s indefiniteness argument appears to the Court to be the same argument it made about the term “injection site hemolysis” in its claim construction briefings, an issue the Court has resolved in a previous Part of this Memorandum. The term “injection site hemolysis” is now properly construed, so Defendant’s indefiniteness argument is moot. The ’802 Patent is not invalid for indefiniteness.

2. *Lack of Enablement and Lack of Written Description.*

Defendant argues that all Asserted Claims in both patents-in-suit are invalid for lack of written description and lack of enablement. Specifically, Defendant argues that the Asserted Claims are invalid for (1) the injection site hemolysis reduction claim (Claims 1, 7, and 18 of the ’802 Patent); (2) the pH limitations (Claims 1 and 18

of the '802 Patent, and Claim 27 of the '105 Patent); (3) the claimed volume range (Claim 18 of the '802 Patent); and (4) the osmolality range (Claim 27 of the '105 Patent).

A patent that fails to include a specification with sufficient specificity such that a POSA can use the invention without too much experimentation based on that specification may be invalid for lack of enablement. 35 U.S.C. § 112(a) (“The specification shall contain . . . the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same . . .”). The accused infringer can successfully hold a patent invalid for lack of enablement by showing that a POSA would not be able to use the claimed invention “without undue experimentation.” *In re Wands*, 858 F.2d 731, 736–37 (Fed. Cir. 1988).

Some experimentation, of course, is permissible. A specification does not need to “describe with particularity how to make and use every single embodiment within a claimed class” and is not inadequate “just because it leaves the skilled artist to engage in some measure of adaptation or testing.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610–11 (2023). A “reasonable amount of experimentation to make and use a patented invention” is expected and will not invalidate the patent. *Id.* at 612. What counts as “reasonable” in any patent case “will depend on the nature of the invention and the underlying art.” *Id.* The question is whether the amount of experimentation required will “detract from the basic statutory requirement that a patent’s specification describe the invention ‘in such full, clear, concise, and exact terms as to enable any

person skilled in the art’ to ‘make and use’ the invention.” *Id.* (quoting 35 U.S.C. § 112(a)).

A patent’s specification that fails to provide a sufficient written description may leave the patent invalid for lack of written description. 35 U.S.C. § 112(a) (“The specification shall contain a written description of the invention.”). This written description “must ‘clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.’” *Ariad Pharms., Inc.*, 598 F.3d at 1351 (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562–63 (Fed. Cir. 1991)). The test for sufficiency of the written description is “whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Id.* The written description in the specification must accurately represent the scope of the patent, not broadening or overreaching the actual scope of the invention. *Id.* at 1353–54.

Defendant first argues that the pH claim elements are invalid for lack of written description and lack of enablement because under some conditions that fall within the scope of the claims, a POSA would not be able to make formulations at some of the claimed pH levels because they would become insoluble and thus unsuitable for intravenous administration. Next, Defendant argues that the osmolality and volume claim elements are invalid for lack of enablement and written description because neither specify a lower limit. According to Defendant, administering the formulation at an osmolality of 0 mOsmol/kg (which would fit

within the claim term of “less than about 500 mOsmol/kg”) or at a volume of 1 mL (which would fit within the claim term of “less than 500 mL”) would be dangerous and unsuitable for intravenous administration. But Defendant’s expert witnesses also testified that a POSA would be able to adjust the intravenous formulation such that it would be administered at an appropriate and safe pH level, osmolality, and injection volume. A POSA would know the appropriate and safe ranges for each element and would adjust them accordingly to ensure that the administered formulation was not insoluble, toxic, or intolerable for the patient. A POSA would never administer—or even consider administering—a drug at a dangerously low osmolality or pH, or a dangerously high injection volume. A POSA would not need to do an unduly amount of experimentation to discover what the appropriate pH, osmolality, and volume should be. A POSA would be able to understand the purpose of the invention and how to use it effectively. Accordingly, the patents-in-suit are not invalid for lack of written description or for lack of enablement.


VI. CONCLUSION

Based on the foregoing findings of fact and conclusions of law, the Court concludes that Plaintiffs have shown by a preponderance of the evidence that Defendant has infringed on the ’105 Patent and the ’802 Patent, and that Defendant has failed to show by clear and convincing evidence that the Asserted Claims of the patents-in-suit are invalid for obviousness, indefiniteness, lack of written description, or lack of enablement. Accordingly, the Court finds that the Asserted Claims of the

'802 Patent and the '105 Patent are valid and enforceable and thus enters judgment in favor of Plaintiffs Melinta and against Defendant Nexus.¹⁴

SO ORDERED in No. 21-cv-02636.

Date: November 15, 2024



JOHN F. KNESS
United States District Judge

¹⁴ For the reasons set forth in this Memorandum, the Court finds for Plaintiffs. But Plaintiffs' litigation position was not so strong, nor was the manner in which Defendant litigated so unreasonable, as to justify this being an "exceptional" case. Accordingly, Plaintiffs are not entitled to an award of reasonable attorneys' fees under 35 U.S.C. § 285. *See Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 572 U.S. 545, 554 (2014) ("an 'exceptional' case is simply one that stands out from others with respect to the substantive strength of a party's litigating position (considering both the governing law and the facts of the case) or the unreasonable manner in which the case was litigated.").

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS

MELINTA THERAPEUTICS, LLC, MELINTA
SUBSIDIARY CORP., and REMPEX
PHARMACEUTICALS, INC.,

Plaintiffs,

v.

NEXUS PHARMACEUTICALS, INC.,

Defendant.

No. 21-cv-02636

Judge John F. Kness

JUDGMENT IN A CIVIL CASE

Judgment is hereby entered (check appropriate box):

- ☐ in favor of Plaintiff(s)
and against Defendant(s)
which ☐ includes pre-judgment interest.
☐ does not include pre-judgment interest.

Post-judgment interest accrues on that amount at the rate provided by law from the date of this judgment.

Plaintiffs shall recover costs from Defendant.

-
- ☐ in favor of Defendant(s)
and against Plaintiff(s)


Defendant(s) shall recover costs from plaintiff(s).

-
- ☒ other: in favor of Plaintiffs Melinta and against Defendant Nexus on Counts II and III of the Complaint and Counts I and II of the Counterclaim. The Court also enters a permanent injunction order, which is appended to this final judgment as Attachment A. Count I of the Complaint is dismissed as moot.
-

This action was (*check one*):

- ☐ tried by a jury with Judge John F. Kness presiding, and the jury has rendered a verdict.
☒ tried by Judge John F. Kness without a jury and the above decision was reached.
☐ decided by Judge John F. Kness on a motion.

Date: November 15, 2024



JOHN F. KNESS
United States District Judge

APPX000126

ATTACHMENT A

**IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION**

MELINTA THERAPEUTICS, LLC,
MELINTA SUBSIDIARY CORP, and
REMPEX PHARMACEUTICALS, INC.,

Plaintiffs,

V.

NEXUS PHARMACEUTICALS, INC.,

Defendant.

No. 21-cv-02636

Judge John F. Kness

PERMANENT INJUNCTION ORDER

Defendant has been found liable of induced and contributory infringement of Claims 1, 7, and 18 of Plaintiffs' Patent No. 9,084,802 and Claim 27 of Plaintiffs' Patent No. 9,278,105. Plaintiffs have proved direct, induced, and contributory infringement by a preponderance of the evidence. Defendant has failed to prove invalidity for obviousness, indefiniteness, lack of enablement, or lack of written description by clear and convincing evidence. For these reasons, the Court finds that permanent injunctive relief enjoining Defendant from manufacturing, using, offering for sale, or selling its ANDA product until the expiration of Plaintiffs' patents is appropriate. 35 U.S.C. §§ 271(a)–(c), (e).

1. Defendant's submission of the ANDA No. 214934 infringed the '802 Patent and the '105 Patent pursuant to 35 U.S.C. § 271(e)(2)(A);
2. The commercial manufacture, use, offer for sale, and / or sale of the ANDA product within the United States, and / or the importation of the ANDA

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS

MELINTA THERAPEUTICS, LLC, MELINTA
SUBSIDIARY CORP., and REMPEX
PHARMACEUTICALS, INC.,

Plaintiffs,

v.

NEXUS PHARMACEUTICALS, INC.,

Defendant.

No. 21-cv-05995

Judge John F. Kness

JUDGMENT IN A CIVIL CASE

Judgment is hereby entered (check appropriate box):

- ☐ in favor of Plaintiff(s)
and against Defendant(s)
which ☐ includes pre-judgment interest.
☐ does not include pre-judgment interest.

Post-judgment interest accrues on that amount at the rate provided by law from the date of this judgment.

Plaintiffs shall recover costs from Defendant.

-
- ☐ in favor of Defendant(s)
and against Plaintiff(s)


Defendant(s) shall recover costs from plaintiff(s).

-
- ☒ other: in favor of Plaintiffs Melinta and against Defendant Nexus on Counts II and III of the Complaint and Counts I and II of the Counterclaim. The Court also enters a permanent injunction order, which is appended to this final judgment as Attachment A. Count I of the Complaint is dismissed as moot.
-

This action was (*check one*):

- ☐ tried by a jury with Judge John F. Kness presiding, and the jury has rendered a verdict.
☒ tried by Judge John F. Kness without a jury and the above decision was reached.
☐ decided by Judge John F. Kness on a motion.

Date: November 15, 2024



JOHN F. KNESS
United States District Judge

APPX000130

ATTACHMENT A

**IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION**

MELINTA THERAPEUTICS, LLC,
MELINTA SUBSIDIARY CORP, and
REMPEX PHARMACEUTICALS, INC.,

Plaintiffs,

V.

NEXUS PHARMACEUTICALS, INC.,

Defendant.

No. 21-cv-05995

Judge John F. Kness

PERMANENT INJUNCTION ORDER

Defendant has been found liable of induced and contributory infringement of Claims 1, 7, and 18 of Plaintiffs' Patent No. 9,084,802 and Claim 27 of Plaintiffs' Patent No. 9,278,105. Plaintiffs have proved direct, induced, and contributory infringement by a preponderance of the evidence. Defendant has failed to prove invalidity for obviousness, indefiniteness, lack of enablement, or lack of written description by clear and convincing evidence. For these reasons, the Court finds that permanent injunctive relief enjoining Defendant from manufacturing, using, offering for sale, or selling its ANDA product until the expiration of Plaintiffs' patents is appropriate. 35 U.S.C. §§ 271(a)–(c), (e).

1. Defendant's submission of the ANDA No. 214934 infringed the '802 Patent and the '105 Patent pursuant to 35 U.S.C. § 271(e)(2)(A);
2. The commercial manufacture, use, offer for sale, and / or sale of the ANDA product within the United States, and / or the importation of the ANDA

**UNITED STATES DISTRICT COURT
FOR THE Northern District of Illinois – CM/ECF NextGen 1.8 (rev. 1.8.1)
Eastern Division**

Melinta Therapeutics, LLC, et al.

Plaintiff,

v.

Case No.: 1:21-cv-02636

Honorable John F. Kness

Nexus Pharmaceuticals, Inc.

Defendant.

NOTIFICATION OF DOCKET ENTRY

This docket entry was made by the Clerk on Friday, November 15, 2024:

MINUTE entry before the Honorable John F. Kness: For the reasons stated in the accompanying opinion, which shall serve as the Court's required findings of fact and conclusions of law under Rule 52 of the Federal Rules of Civil Procedure, the Court holds that Plaintiffs have proven by a preponderance of the evidence that Defendant has infringed on its patents (Counts II and III), and Defendant has failed to prove by clear and convincing evidence that Plaintiffs' patents are invalid (Counts I and II of the counterclaim). Count I of the Complaint is dismissed as moot. Enter separate findings of fact and conclusions of law. Enter separate final judgment order with an appended permanent injunction order. The Court offers its sincere gratitude to counsel for both parties for their well-presented arguments. Civil case terminated. Mailed notice. (exr,)

ATTENTION: This notice is being sent pursuant to Rule 77(d) of the Federal Rules of Civil Procedure or Rule 49(c) of the Federal Rules of Criminal Procedure. It was generated by CM/ECF, the automated docketing system used to maintain the civil and criminal dockets of this District. If a minute order or other document is enclosed, please refer to it for additional information.

For scheduled events, motion practices, recent opinions and other information, visit our web site at www.ilnd.uscourts.gov.

**UNITED STATES DISTRICT COURT
FOR THE Northern District of Illinois – CM/ECF NextGen 1.8 (rev. 1.8.1)
Eastern Division**

Melinta Therapeutics, LLC, et al.

Plaintiff,

v.

Case No.: 1:21-cv-05995

Honorable John F. Kness

Nexus pharmaceuticals, Inc., et al.

Defendant.

NOTIFICATION OF DOCKET ENTRY

This docket entry was made by the Clerk on Friday, November 15, 2024:

MINUTE entry before the Honorable John F. Kness: This action is a companion case to Case No. 21-cv-02636, which was tried to the Court on a bench trial from June 6, 2023 to June 9, 2023. By separate orders in related case no. 21-cv-2636, the Court entered Findings of Fact and Conclusions of Law, and a final judgment in Plaintiffs' favor. In the time since the cases were consolidated on 12/07/2021, neither party has addressed this companion action, nor suggested or offered a suggestion that it remains open or different than 21-cv-2636 in any way. Accordingly, the Court will enter a final judgment in this companion case identical to the final judgment it entered in 21-cv-2636 and terminate this case. If the parties believe that the Court has misapprehended the status of this companion case in any way, they may file an appropriate motion. Mailed notice. (exr,)

ATTENTION: This notice is being sent pursuant to Rule 77(d) of the Federal Rules of Civil Procedure or Rule 49(c) of the Federal Rules of Criminal Procedure. It was generated by CM/ECF, the automated docketing system used to maintain the civil and criminal dockets of this District. If a minute order or other document is enclosed, please refer to it for additional information.

For scheduled events, motion practices, recent opinions and other information, visit our web site at www.ilnd.uscourts.gov.

(12) **United States Patent**
Griffith et al.

(10) **Patent No.:** **US 9,084,802 B2**
(45) **Date of Patent:** **Jul. 21, 2015**

(54) **TETRACYCLINE COMPOSITIONS**

(71) Applicant: **Rempex Pharmaceuticals, Inc.**, San Diego, CA (US)

(72) Inventors: **David C. Griffith**, San Marcos, CA (US); **Serge Boyer**, San Diego, CA (US); **Scott Hecker**, Del Mar, CA (US); **Michael N. Dudley**, San Diego, CA (US)

(73) Assignee: **REMPEX PHARMACEUTICALS, INC.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/204,881**

(22) Filed: **Mar. 11, 2014**

(65) **Prior Publication Data**

US 2014/0194393 A1 Jul. 10, 2014

Related U.S. Application Data

(60) Division of application No. 13/654,018, filed on Oct. 17, 2012, which is a continuation of application No. PCT/US2011/036351, filed on May 12, 2011.

(60) Provisional application No. 61/392,304, filed on Oct. 12, 2010, provisional application No. 61/334,106, filed on May 12, 2010.

(51) **Int. Cl.**

A01N 47/00 (2006.01)
A61K 31/21 (2006.01)
A61K 31/65 (2006.01)
A61K 9/00 (2006.01)
A61K 47/02 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 31/65** (2013.01); **A61K 9/0019** (2013.01); **A61K 47/02** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Craig Ricci

Assistant Examiner — Jared D Barsky

(74) *Attorney, Agent, or Firm* — Knobbe Martens Olson & Bear LLP

(57) **ABSTRACT**

The present invention relates to compositions, pharmaceutical compositions, and methods for preparing the same, comprising a tetracycline with improved stability and solubility. Some embodiments include a tetracycline with an excess of a divalent or trivalent cation.

31 Claims, 7 Drawing Sheets

Melinta v. Nexus
21-cv-02636

PTX 1

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APPX000137

QPEx001490

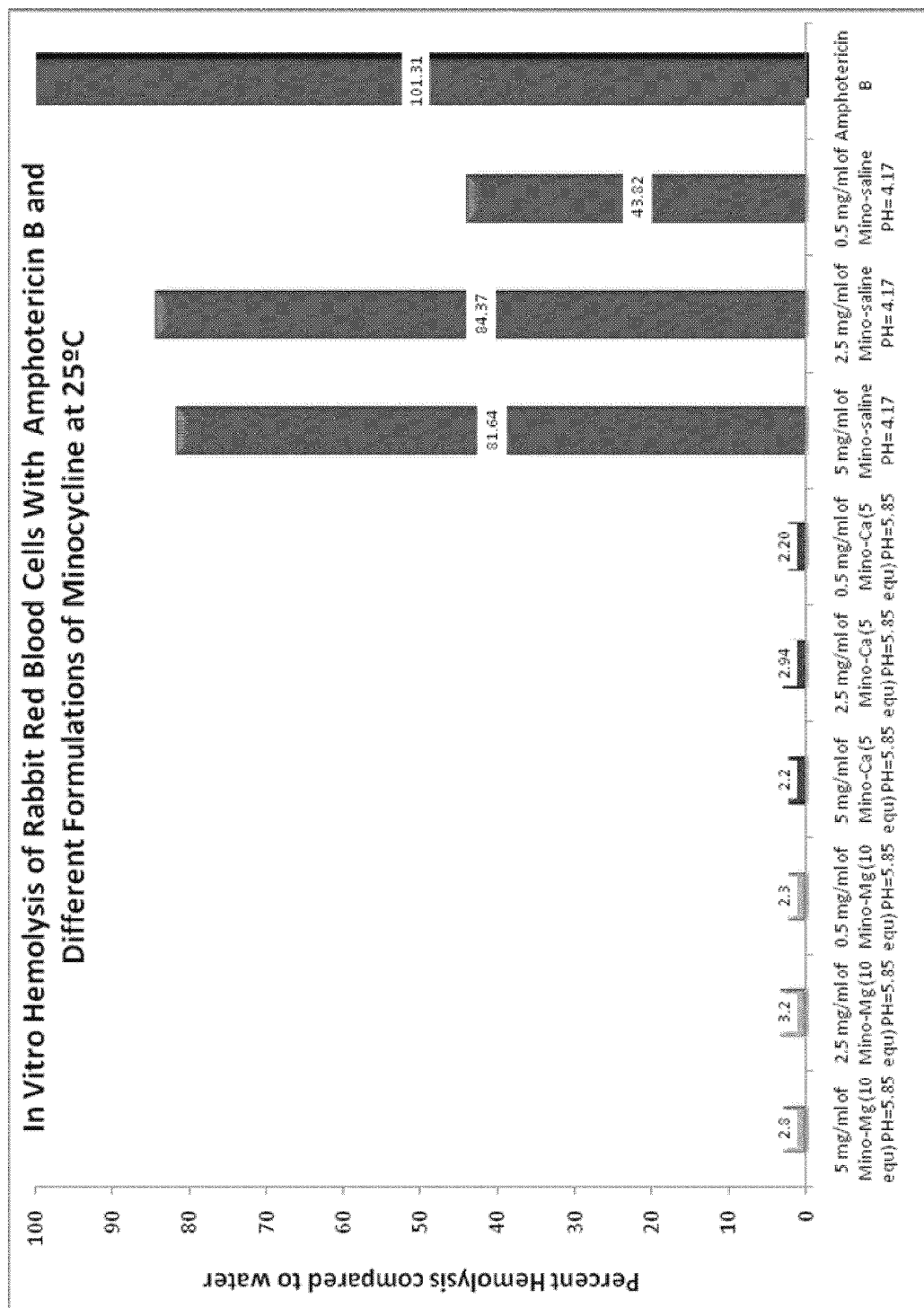


FIG. 1

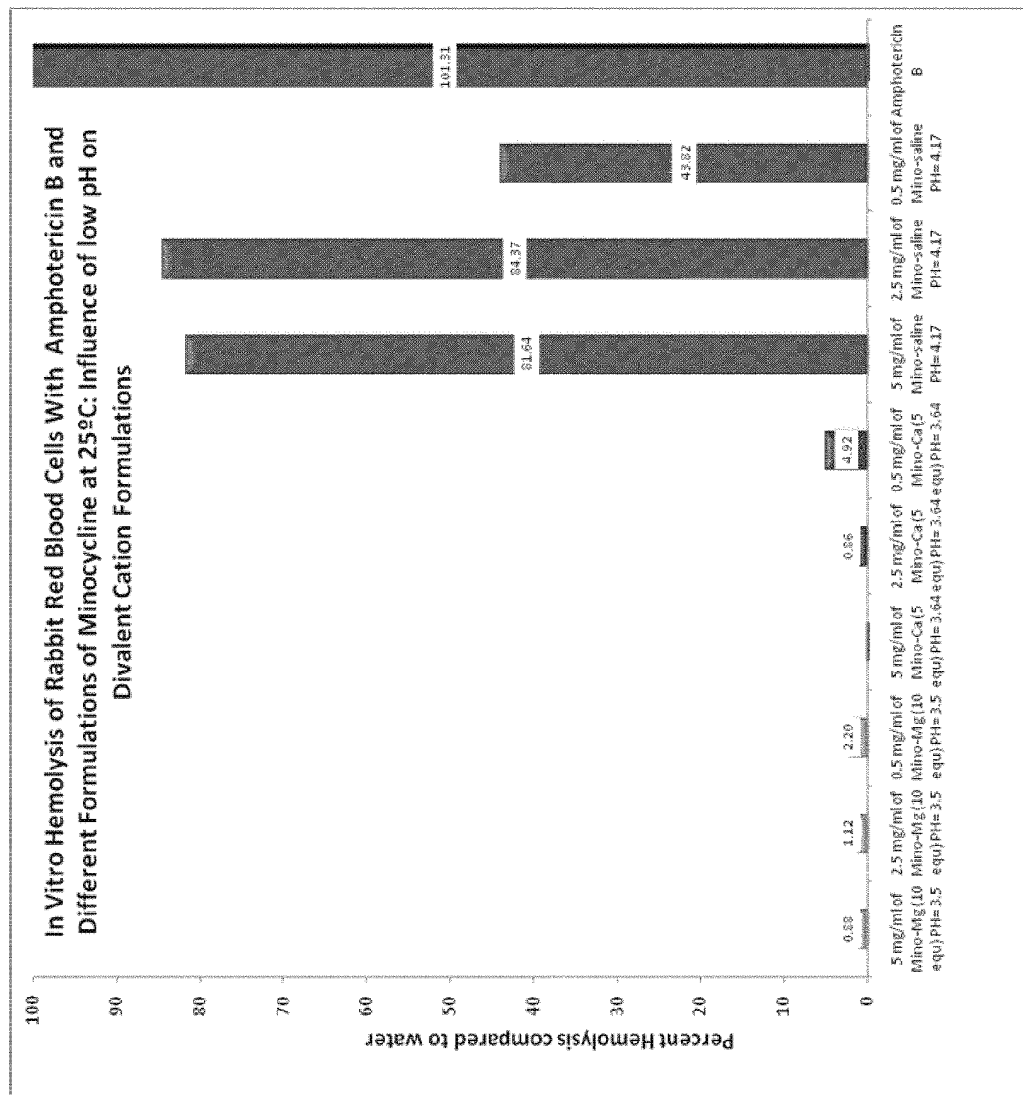


FIG. 2

Rabbit Red Blood Cell Hemolysis Produced by 2.5 mg/ml of Minocin compared to Mino-Mg (using MgSO_4)

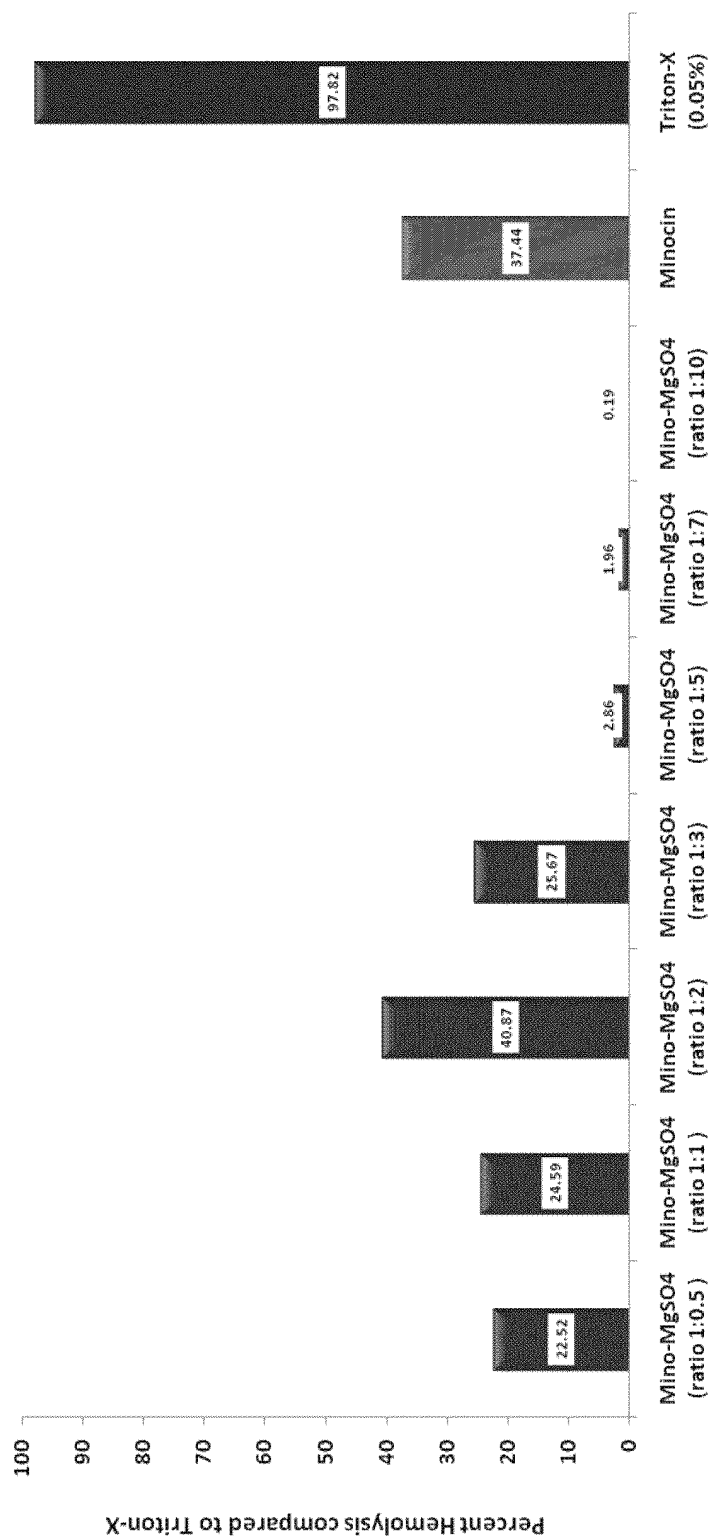


FIG. 3

Rabbit Red Blood Cell Hemolysis Produced by 2.5 mg/ml of Minocin compared to Mino-Mg (using $MgCl_2$)

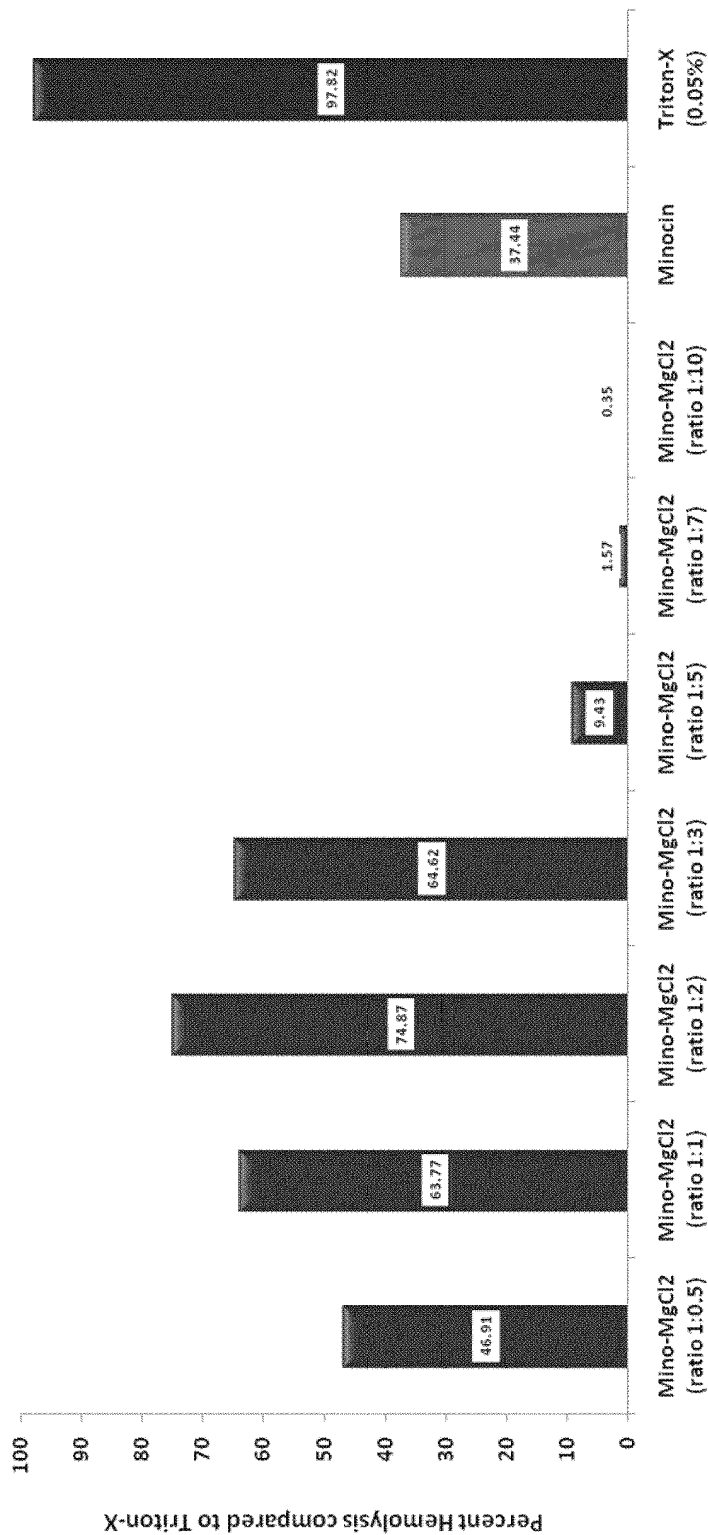


FIG. 4

Rabbit Red Blood Cell Hemolysis Produced by 2.5 mg/ml of Minocin compared to Mino-Ca (using CaCl_2)

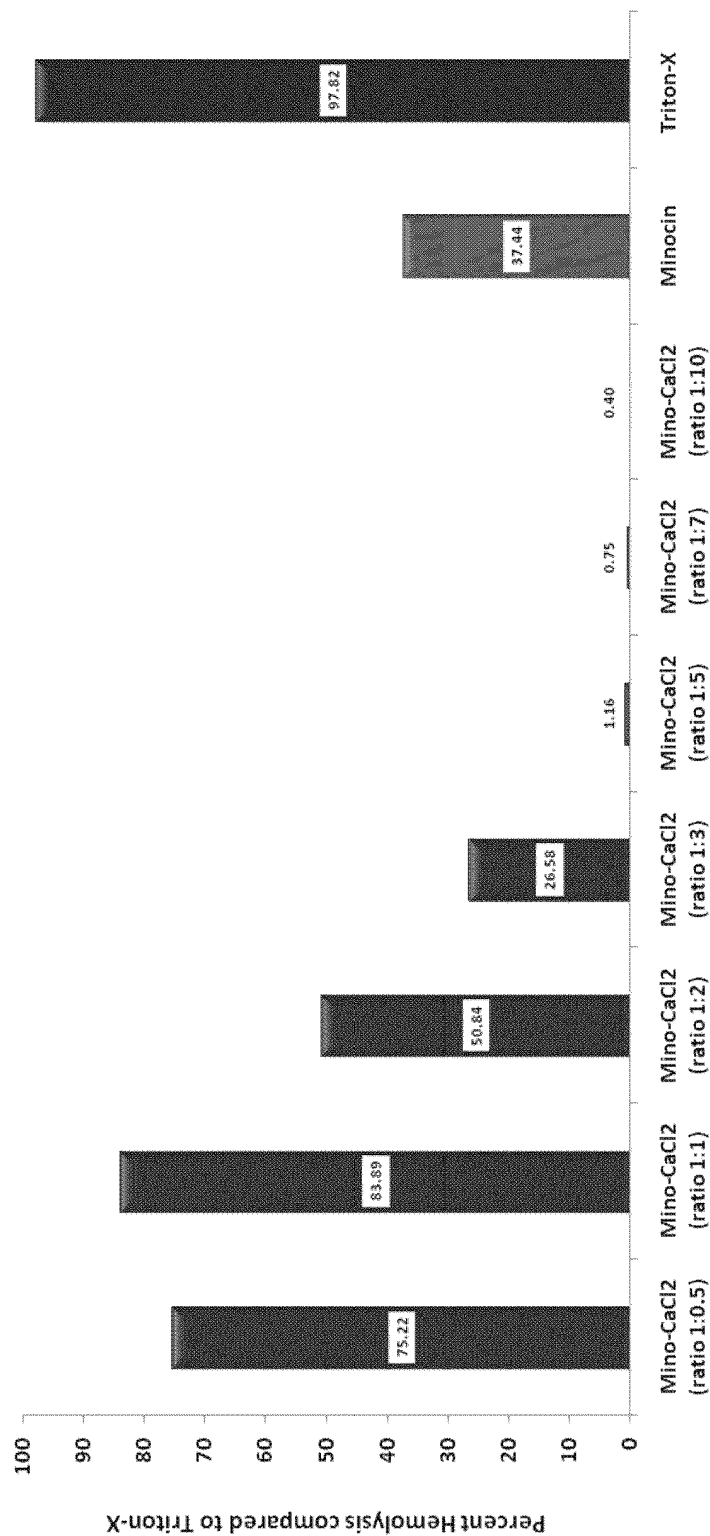


FIG. 5

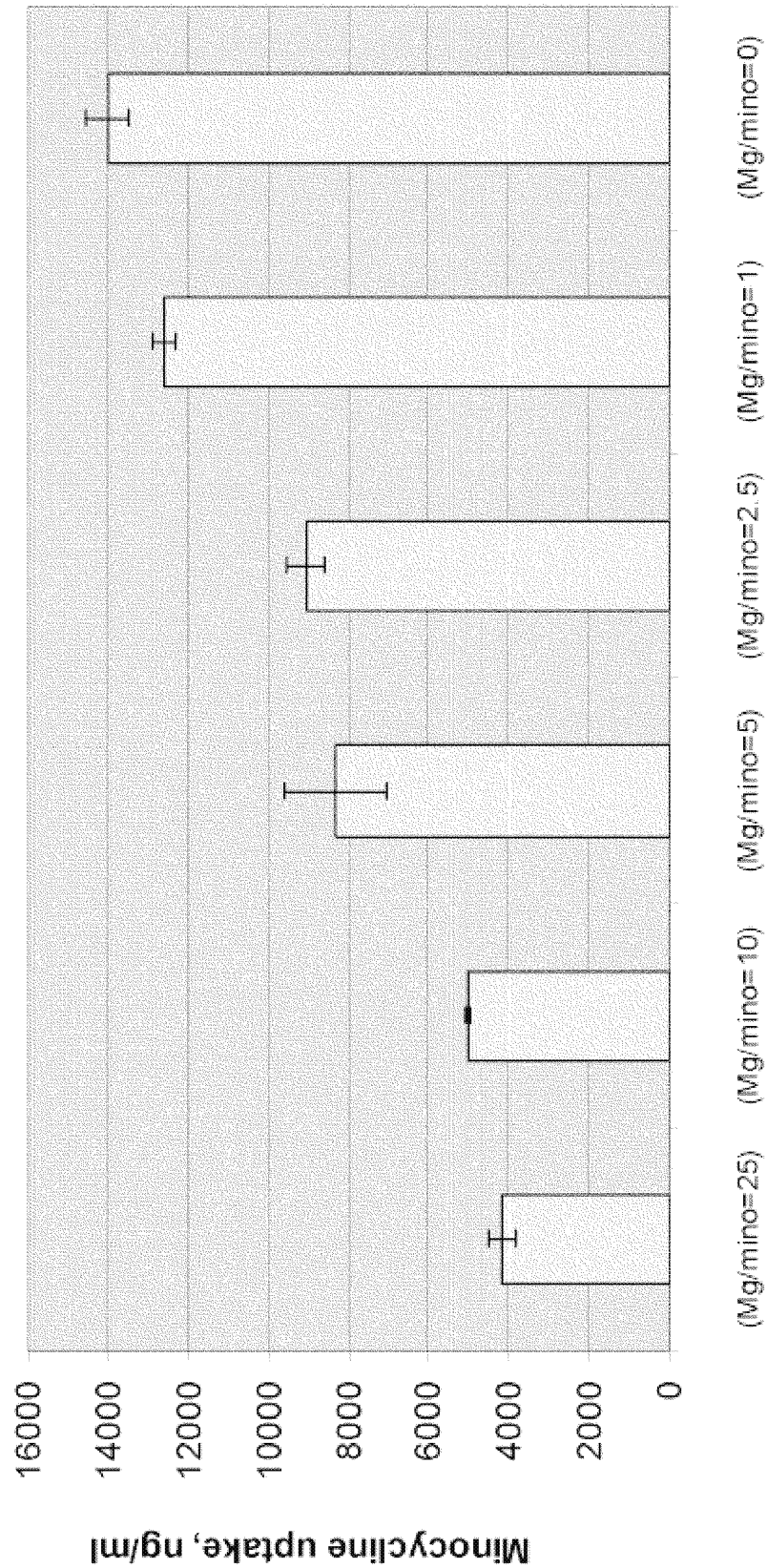


FIG. 6

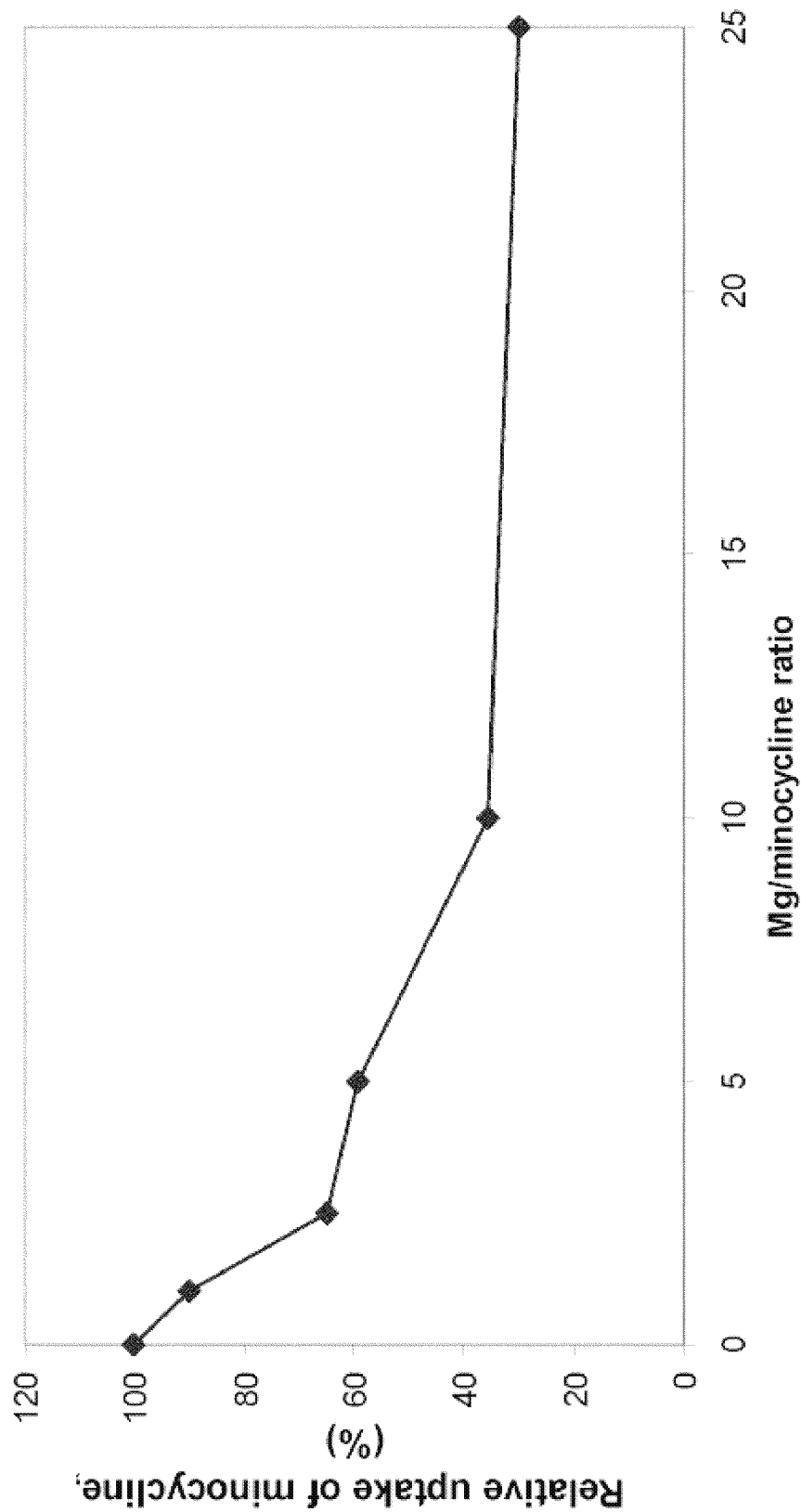


FIG. 7

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TETRACYCLINE COMPOSITIONS

RELATED APPLICATIONS

This application is a division of U.S. application Ser. No. 13/654,018 filed Oct. 17, 2012 which is a continuation of International Application No. PCT/US2011/036351 filed on May 12, 2011, which claims priority to U.S. Provisional Application No. 61/392,304 filed Oct. 12, 2010, and to U.S. Provisional Application No. 61/334,106 filed May 12, 2010, the contents of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to tetracycline compositions and methods for preparing and using the same. Some embodiments include a tetracycline with an excess of a divalent or trivalent cation.

BACKGROUND OF THE INVENTION

Tetracyclines are used as broad spectrum antibiotics to treat various bacterial infections, such as infections of the respiratory tract, sinuses, middle ear, urinary tract, and intestines, and can be used in the treatment of gonorrhoea, especially in patients allergic to β -lactams and macrolides. Tetracyclines interfere with the protein synthesis of Gram positive and Gram-negative bacteria by preventing the binding of aminoacyl-tRNA to the ribosome. The action of tetracyclines is bacteriostatic (preventing growth of bacteria) rather than killing (bactericidal).

Tetracyclines degrade rapidly to form epitetracycline, anhydrotetracycline, epianhydrotetracycline, and other degradation products. Once degraded, tetracyclines have small therapeutic value, since the degradation products have no therapeutically useful activity. Degradation begins as soon as the antibiotic is in solution, and continues until reaching an equilibrium of antibiotic and epimer concentrations. The equilibrium point is temperature and pH dependent, with more epimer being formed at higher temperatures and lower pH. Oxidation and other side reactions cause further degradation. Thus, tetracyclines can have a limited existence in aqueous environments in their active form. Moreover, the degradation products of tetracyclines are toxic and can cause Fanconi syndrome, a potentially fatal disease affecting proximal tubular function in the nephrons of the kidneys.

There is a need to provide hospital staff with the flexibility and advantages that come with longer admixture and reconstitution times without the need for refrigeration so that for instance, a hospital pharmacist could prepare a solution the day before it is needed. Furthermore, often after a natural disaster such as hurricanes, earthquakes, or tsunamis, access to refrigeration equipment can be scarce and may be further impeded by the lack of electricity. Stable formulations of tetracyclines could be stored as a solution, negating the need for reconstitution, and allowing its use in inhalers or nebulizers for outpatient use.

In addition, some tetracyclines can cause tetracycline-induced hemolysis. This hemolysis can lead to venous phlebitis at the site of injection when administered intravenously, resulting in irritation and potentially limiting the volumes of infusion that can be tolerated. Thus, there is a need for formulations of such tetracyclines that reduce the incidence of hemolysis.

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SUMMARY OF THE INVENTION

The present invention relates to tetracycline compositions and methods for preparing and using the same. Some embodiments include a tetracycline with an excess of a divalent or trivalent cation.

Some embodiments include pharmaceutical compositions. In some embodiments the pharmaceutical compositions comprise an aqueous solution of minocycline and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to minocycline is greater than 2:1 and wherein the solution does not comprise a pharmaceutically acceptable oil and is suitable for intravenous administration.

In some embodiments the pharmaceutical compositions comprise an aqueous solution of minocycline and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to minocycline is greater than 2:1 and wherein the solution has a pH greater than 4 and less than 5 and is suitable for intravenous administration.

In some embodiments the pharmaceutical compositions comprise an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and wherein the solution does not comprise a pharmaceutically acceptable oil, gluconate, or a pyridine-containing compound, has a pH greater than 2 and less than 7, and is suitable for intravenous administration.

In some embodiments, the solution does not comprise polyoxyethylene hydrogenated castor oil.

In some embodiments, the solution does not comprise an antioxidant.

In some embodiments, the solution does not comprise a pyridine-containing compound.

In some embodiments, the solution does not comprise nicotinamide.

In some embodiments, the solution does not comprise an alcohol.

In some embodiments, the solution does not comprise glycerol.

In some embodiments, the solution does not comprise polyethylene glycol.

In some embodiments, the solution does not comprise gluconate.

In some embodiments, the solution does not comprise a pyrrolidone compound.

In some embodiments, the solution does not comprise a water-miscible local anaesthetic.

In some embodiments, the water-miscible local anaesthetic is procaine.

In some embodiments, the solution does not comprise urea.

In some embodiments, the solution does not comprise lactose.

In some embodiments, the solution does not comprise a dehydrating agent. In some embodiments, the dehydrating agent is selected from the group consisting of ethyl acetate, acetic anhydride, absolute ethanol, ethyl acetate, acetic anhydride, and mixtures thereof.

In some embodiments, the solution has a pH of less than 7.

In some embodiments, the solution has a pH of less than 6.

In some embodiments, the solution has a pH of less than 5.

In some embodiments, the solution has a pH greater than 2 and less than 7. In some embodiments, the solution has a pH greater than 4 and less than 7. In some embodiments, the solution has a pH greater than 4 and less than 6. In some embodiments, the solution has a pH greater than 4 and less than 5.

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In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 3:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 5:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 8:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 10:1.

In some embodiments, the osmolality of the solution is less than 500 mOsm/kg. In some embodiments, the osmolality of the solution is less than 400 mOsm/kg. In some embodiments, the osmolality of the solution is less than 350 mOsm/kg.

In some embodiments, the concentration of minocycline is at least 1 mg/ml. In some embodiments, the concentration of minocycline is at least 5 mg/ml. In some embodiments, the concentration of minocycline is at least 10 mg/ml.

In some embodiments, the solution comprises magnesium sulfate. In some embodiments, the solution comprises magnesium oxide. In some embodiments, the solution comprises magnesium acetate. In some embodiments, the solution comprises magnesium chloride.

In some embodiments, the solution comprises a buffer. In some embodiments, the solution comprises acetate.

In some embodiments, the solution comprises a base. In some embodiments, the base comprises NaOH.

In some embodiments, the cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In some embodiments, the cation is selected from magnesium, calcium, and zinc. In some embodiments, the cation is magnesium.

In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylicycline. In some embodiments, the glycylicycline is tigecycline. In some embodiments, the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the 7-dimethylamino-tetracycline is PTK796.

Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline, MgCl_2 , and NaOH, wherein the Mg to minocycline molar ratio is 5:1, and the pH is greater than 4.5 and less than 5.5.

Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline, MgSO_4 , and sodium acetate, wherein the Mg to minocycline molar ratio is 5:1, the pH is greater than 4.5 and less than 5.5, and the osmolality is greater than 275 mOsm/kg and less than 375 mOsm/kg.

Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline and $\text{Mg}(\text{C}_2\text{H}_3\text{O}_2)_2$, wherein the Mg to minocycline molar ratio is 5:1, and the pH is greater than 4.5 and less than 5.5.

Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline, MgSO_4 , and NaOH, wherein the Mg to minocycline molar ratio is 5:1, the pH is greater than 4.5 and less than 5.5, and the osmolality is greater than 150 mOsm/kg and less than 250 mOsm/kg.

Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 5.5 and less than 6.5.

Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 5.5 and less than 6.5.

Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, MgCl_2 , and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 5.5 and less than 6.5.

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Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, MgCl_2 , and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 5.5 and less than 6.5.

Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tigecycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 6.0 and less than 7.0.

Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tigecycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 6.0 and less than 7.0.

Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tigecycline, CaCl_2 , and NaOH, wherein the Ca to tigecycline molar ratio is 5:1, and the pH is greater than 6.0 and less than 7.0.

Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tigecycline, CaCl_2 , and NaOH, wherein the Ca to tigecycline molar ratio is 12:1, and the pH is greater than 6.0 and less than 7.0.

Some embodiments include water-soluble solid compositions comprising minocycline or a salt thereof and a salt that comprises a divalent or trivalent cation.

Some embodiments include water-soluble solid compositions comprising a 7-dimethylamino-tetracycline antibiotic or a salt thereof and a salt comprising a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and wherein the composition does not comprise gluconate or a pyridine-containing compound.

In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 1:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 2:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 3:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 5:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is at greater than 8:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 10:1.

Some embodiments include compositions in the form of a lyophile.

In some embodiments, the salt is magnesium sulfate.

In some embodiments, the salt is calcium chloride.

In some embodiments, the composition comprises sodium acetate.

In some embodiments, the composition comprises NaOH.

In some embodiments, the salt is selected from magnesium chloride, magnesium bromide, magnesium sulfate, calcium chloride, calcium bromide, calcium sulfate, zinc chloride, gallium chloride, magnesium malate, magnesium citrate, magnesium acetate, calcium citrate, zinc acetate, and zinc citrate.

In some embodiments, the composition does not comprise an antioxidant.

In some embodiments, the composition does not comprise a pyridine-containing compound. In some embodiments, the composition does not comprise nicotinamide.

In some embodiments, the composition does not comprise gluconate.

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In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline. In some embodiments, the glycylcycline is tigecycline. In some embodiments, the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the 7-dimethylamino-tetracycline is PTK796.

Some embodiments include methods for preparing a pharmaceutical composition comprising dissolving the water-soluble solid composition of any one of the water-soluble solid compositions provided herein in water to form a solution

Some embodiments include methods for preparing a pharmaceutical composition comprising dissolving a 7-dimethylamino-tetracycline in a solution comprising a divalent or trivalent cation.

Some embodiments include methods for preparing a pharmaceutical composition comprising dissolving a 7-dimethylamino-tetracycline in a solution comprising a divalent or trivalent cation; adjusting the pH of the solution; and lyophilizing the composition.

In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline. In some embodiments, the glycylcycline is tigecycline.

In some embodiments, the pH of the solution is adjusted to be less than 6. In some embodiments, the pH of the solution is adjusted to be less than 5.

In some embodiments, the pH of the solution is adjusted to be greater than 2 and less than 7. In some embodiments, the pH of the solution is adjusted to be greater than 4 and less than 7. In some embodiments, the pH of the solution is adjusted to be greater than 4 and less than 6. In some embodiments, the pH of the solution is adjusted to be greater than 4 and less than 5.

In some embodiments, adjusting the pH comprises adding an acid. In some embodiments, the acid is HCl.

In some embodiments, adjusting the pH comprises adding a base. In some embodiments, the base is NaOH.

In some embodiments, adjusting the pH comprises forming a buffer. In some embodiments, forming the buffer comprises adding sodium acetate.

In some embodiments, the divalent or trivalent cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In some embodiments, the cation is selected from magnesium, calcium, and zinc. In some embodiments, the cation is magnesium.

Some embodiments include kits comprising a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises minocycline in an amount such that the molar ratio of the divalent or trivalent cation to minocycline is greater than 2:1.

Some embodiments include kits comprising a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises a 7-dimethylamino-tetracycline antibiotic in an amount such that the molar ratio of the divalent or trivalent cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1.

In some embodiments, the diluent comprises an acid. In some embodiments, the acid is HCl.

In some embodiments, the diluent comprises a base. In some embodiments, the base is NaOH.

In some embodiments, the diluent comprises a buffer. In some embodiments, the diluent comprises sodium acetate.

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In some embodiments, the pH of the diluent is greater than pH 6 and less than pH 8.

In some embodiments, the divalent or trivalent cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In some embodiments, the cation is selected from magnesium, calcium, and zinc. In some embodiments, the cation is magnesium.

In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 3:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 5:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is at greater than 8:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 10:1.

In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline. In some embodiments, the glycylcycline is tigecycline. In some embodiments, the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the 7-dimethylamino-tetracycline is PTK796.

Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition of any one of the pharmaceutical compositions provided herein to the subject via an intravenous route.

Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition made according to any one of the methods of preparing a pharmaceutical compositions provided herein to the subject via an intravenous route.

In some embodiments, the intravenous administration includes administering less than 200 ml of the composition.

In some embodiments, the intravenous administration includes administering the composition in less than 60 minutes.

Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition of any one of the pharmaceutical compositions provided herein to the subject via a topical route.

Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition made according to any one of the methods of preparing a pharmaceutical compositions provided herein to the subject via a topical route.

Some embodiments include compositions comprising tigecycline and a divalent or trivalent cation, wherein the molar ratio of said divalent or trivalent cation to said tigecycline is greater than 1:1.

In some embodiments, the tigecycline and divalent or trivalent cation are in aqueous solution.

In some embodiments, the molar ratio of said divalent or trivalent cation to said tigecycline is greater than 3:1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a graph of percent hemolysis of rabbit red blood cells incubated with various concentrations of minocycline in various solutions relative to hemolysis in water, in which the minocycline solutions formulated with divalent cations were adjusted to pH 5.85.

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FIG. 2 shows a graph of percent hemolysis of rabbit red blood cells incubated with various concentrations of minocycline in various solutions relative to hemolysis in water.

FIG. 3 depicts a graph of rabbit RBC hemolysis caused by minocycline formulated in different ratios of MgSO_4 .

FIG. 4 depicts a graph of rabbit RBC hemolysis caused by minocycline formulated in different ratios of MgCl_2 .

FIG. 5 depicts a graph of rabbit RBC hemolysis caused by minocycline formulated in different ratios of CaCl_2 .

FIG. 6 depicts a graph for minocycline uptake by HVEC at various concentrations of divalent cation.

FIG. 7 depicts a graph for minocycline uptake by HVEC at various concentrations of divalent cation.

DETAILED DESCRIPTION

The present invention relates to tetracycline compositions and methods for preparing and using the same. Some embodiments include a tetracycline with an excess of a metal cation. In some embodiments, the compositions have improved stability against both oxidative degradation and epimerization. Some such compositions are therefore more stable when dissolved, lyophilized, reconstituted, and/or diluted than other compositions. Some embodiments also provide compositions having a lower level of tetracycline-induced hemolysis and resulting phlebitis.

It was unexpectedly discovered that the incidence of tetracycline-induced hemolysis can be greatly decreased by formulating the tetracycline with divalent or trivalent cations. In some embodiments, high molar ratios of divalent or trivalent cations to tetracycline antibiotics significantly decreases hemolysis.

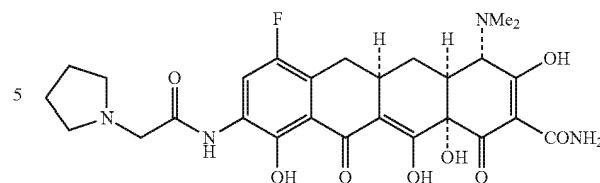
It was also unexpectedly discovered that the stability of aqueous solutions of tetracyclines can be greatly increased by the addition of divalent or trivalent cations. In some embodiments, the stability of aqueous solutions of tetracyclines increase with higher molar ratios of divalent or trivalent cations to tetracycline. Indeed, some such solutions were found to be stable for several weeks at 37° C.

In certain compositions, the solubility of a tetracycline antibiotic is decreased in an aqueous solution comprising a multivalent cation. It has been unexpectedly discovered that increasing the molar ratio of multivalent cation to such tetracycline antibiotics can increase the solubility of the tetracycline. Accordingly, some embodiments described herein provide solutions of a tetracycline with improved solubility.

Compositions

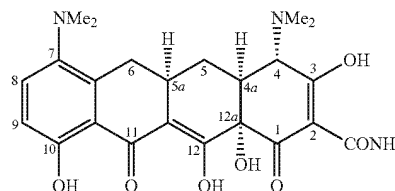
Some embodiments include compositions comprising a tetracycline antibiotic or a salt thereof in combination with a divalent or trivalent cation. Tetracyclines include a family of structurally-related compounds that may have broad-spectrum antibiotic activities. Examples of tetracyclines include Tetracycline, Chlortetracycline, Oxytetracycline, Demeclocycline, Doxycycline, Lymecycline, Meclocycline, Methacycline, Minocycline, Rolitetracycline, Minocycline, Tigecycline, Chlorocycline, Glycylcyclines, Aminomethylcyclines, TP434, and PTK796, (also known as BAY 73-7388 and MK2764). The structure of TP434 is provided below:

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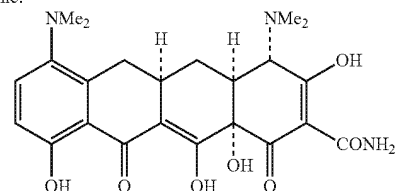
In one embodiment, the tetracycline antibiotic is selected from the group consisting of tetracycline, oxytetracycline, doxycycline, chlorocycline, minocycline, glycylcyclines and aminomethylcyclines. In one embodiment, the tetracycline is a glycylcycline. In one embodiment, the glycylcycline is tigecycline. In one embodiment, the tetracycline is an aminomethylcycline. In one embodiment, the aminomethylcycline is PTK796, also known as BAY 73-7388 and MK2764. In another embodiment, the tetracycline is selected from the group consisting of tetracycline, minocycline, tigecycline and PTK796. In one embodiment, the tetracycline antibiotic is tetracycline. In one embodiment, of the invention, the tetracycline is minocycline. In one embodiment, of the invention, the tetracycline is tigecycline. In yet another embodiment, of the invention, the tetracycline is PTK796. Some embodiments include a salt of a tetracycline antibiotic.

In some embodiments, the tetracycline antibiotic is a 7-dimethylamino-tetracycline. 7-dimethylamino-tetracyclines contain an additional dimethylamino substituent at the 7-position on the four-ring core. The 7-position is indicated on following numbered structure of minocycline:

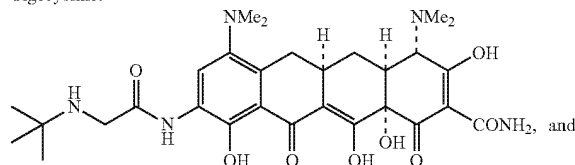


Examples of 7-dimethylamino-tetracyclines include minocycline, a glycylcycline (e.g., tigecycline) and PTK796. Example structures of such compounds include:

Minocycline:



Tigecycline:



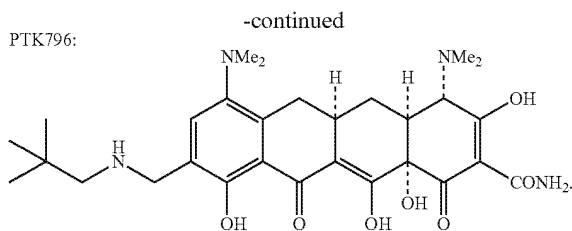
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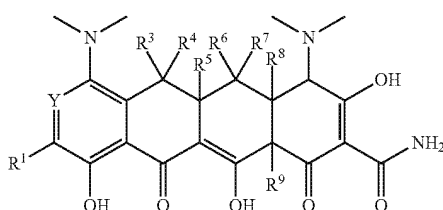
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PTK796:



As used herein, “glycylcyclines” are 7-dimethylamino-tetracyclines having an N-alkylglycylamido side chain at position 9 of the four-ring core.

In some embodiments, the 7-dimethylamino-tetracycline antibiotic has the structure:



or tautomers thereof, wherein:

R¹ is selected from H, $-(CH_2)_nNHC(O)(CH_2)_nR^{10}$, and $-(CH_2)_nR^{10}$, where each n is independently an integer from 0 to 3, and

R¹⁰ is selected from $-NH-C_{1-8}alkyl$, $-NH-C_{1-8}cycloalkyl$, and a saturated 4-to-7-membered heterocycle containing one nitrogen atom, wherein if the connecting atom of R¹⁰ is carbon, the nitrogen atom is optionally substituted by C₁₋₄alkyl;

Y is CR² or N; and

R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from H, $-OH$, halogen, and C₁₋₄ alkyl; or optionally R¹ and R² together form a 6-membered aryl or heteroaryl ring, optionally substituted by one or two groups independently selected from H, R¹, $-OH$, halogen, and C₁₋₄ alkyl.

In some embodiments, each of R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are hydrogen.

As used herein, “alkyl” refers to a straight- or branched-chain moiety containing only carbon and hydrogen. Alkyls may have any degree of saturation. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tertbutyl.

As used herein, “cycloalkyl” refers to a ring or ring system comprising only carbon in the ring backbone. Cycloalkyls may include one or more fused or bridged rings. Cycloalkyls may have any degree of saturation provided that at least one ring is not aromatic. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexenyl.

As used herein, “heterocycle” refers to a ring or ring system comprising at least one heteroatom in the ring backbone. Heterocycles may include one or more fused or bridged rings. Heterocycles may have any degree of saturation provided that at least one ring is not aromatic. Examples include pyrrolidine, piperidine, piperazine, and morpholino.

As used herein, “aryl” refers to an aromatic ring or ring system comprising only carbon in the ring backbone. Aryls may include one or more fused rings. Examples include phenyl and naphthyl.

As used herein, “heteroaryl” refers to an aromatic ring or ring system comprising at least one heteroatom in the ring

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backbone. Heteroaryls may include one or more fused rings. Examples include imidazole, oxazole, pyridine, and quinoline.

Some compositions include at least one multivalent cation.

5 Multivalent cations include bivalent and trivalent cations, e.g., metal cations. The metal cations include common multivalent metal cations. In some embodiments, the metal cations include iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium.

10 Some compositions include a salt that comprises the cation. In one embodiment, the salts are inorganic metal salts and can include anhydrous, hydrated and solvated forms of the salts. In another embodiment, the salts are organic metal salts and include but are not limited to the anhydrous, hydrated and solvated forms of the salt. In one embodiment, the anion in the inorganic metal salts can include chloride, bromide, oxide, and sulfate salts. In one embodiment, the organic metal salts are those where the anion of the salt is selected from the GRAS (generally regarded as safe) list such as but not limited to acetate, citrate, gluconate, and malate salts. Suitable anions may also be found in see Remington’s Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. In some

embodiments, a composition can include more than one type of metal cation. In some such embodiments, the anions for each metal salt can be the same. In another embodiment, the anions for each metal salt are different. In another embodiment, the metal cation is included in the compositions provided herein as different salts of the same cation. In one embodiment the metal salts are all inorganic. In another embodiment, the metal salts are all organic. In yet another embodiment, the metal salts are a combination of organic and inorganic salts.

20 Examples of inorganic metal salts that may be included in the compositions provided herein include magnesium chloride (including the hexahydrate), magnesium bromide, magnesium sulfate (including the heptahydrate), magnesium oxide, calcium chloride, calcium bromide, calcium sulfate, zinc chloride, and gallium chloride. Examples of inorganic metal salts that may be included in the compositions provided herein include magnesium malate, magnesium gluconate, magnesium citrate, magnesium acetate (including the trihydrate), calcium gluconate, calcium citrate, zinc gluconate, zinc acetate, and zinc citrate. The salts described herein include both their anhydrous and hydrated forms.

25 Some compositions provided herein include a tetracycline and divalent or trivalent cation, e.g., metal cation at particular molar ratios of divalent or trivalent cation to tetracycline. For example, some embodiments include compositions comprising a tetracycline and a divalent or trivalent cation, wherein the molar ratio of said divalent or trivalent cation to said tetracycline is greater than about 1:1. In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is greater than about 2:1, greater than about 3:1, greater than about 4:1, greater than about 5:1, greater than about 6:1, greater than about 7:1, greater than about 8:1, greater than about 9:1, greater than about 10:1, greater than about 11:1, greater than about 12:1, greater than about 13:1, greater than about 14:1, greater than about 15:1, greater than about 16:1, greater than about 17:1, greater than about 18:1, greater than about 19:1, greater than about 20:1, greater than about 21:1, greater than about 22:1, greater than about 23:1, greater than about 24:1, greater than about 25:1, greater than about 26:1, greater than about 27:1, greater than about 28:1, greater than about 29:1, and greater than about 30:1. In some

embodiments, the molar ratio is greater than about 35:1, greater than about 40:1, greater than about 45:1, and greater than about 50:1.

35 Examples of inorganic metal salts that may be included in the compositions provided herein include magnesium chloride (including the hexahydrate), magnesium bromide, magnesium sulfate (including the heptahydrate), magnesium oxide, calcium chloride, calcium bromide, calcium sulfate, zinc chloride, and gallium chloride. Examples of inorganic metal salts that may be included in the compositions provided herein include magnesium malate, magnesium gluconate, magnesium citrate, magnesium acetate (including the trihydrate), calcium gluconate, calcium citrate, zinc gluconate, zinc acetate, and zinc citrate. The salts described herein include both their anhydrous and hydrated forms.

40 Some compositions provided herein include a tetracycline and divalent or trivalent cation, e.g., metal cation at particular molar ratios of divalent or trivalent cation to tetracycline. For example, some embodiments include compositions comprising a tetracycline and a divalent or trivalent cation, wherein the molar ratio of said divalent or trivalent cation to said tetracycline is greater than about 1:1. In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is greater than about 2:1, greater than about 3:1, greater than about 4:1, greater than about 5:1, greater than about 6:1, greater than about 7:1, greater than about 8:1, greater than about 9:1, greater than about 10:1, greater than about 11:1, greater than about 12:1, greater than about 13:1, greater than about 14:1, greater than about 15:1, greater than about 16:1, greater than about 17:1, greater than about 18:1, greater than about 19:1, greater than about 20:1, greater than about 21:1, greater than about 22:1, greater than about 23:1, greater than about 24:1, greater than about 25:1, greater than about 26:1, greater than about 27:1, greater than about 28:1, greater than about 29:1, and greater than about 30:1. In some

embodiments, the molar ratio is greater than about 35:1, greater than about 40:1, greater than about 45:1, and greater than about 50:1.

45 Some compositions provided herein include a tetracycline and divalent or trivalent cation, e.g., metal cation at particular molar ratios of divalent or trivalent cation to tetracycline. For example, some embodiments include compositions comprising a tetracycline and a divalent or trivalent cation, wherein the molar ratio of said divalent or trivalent cation to said tetracycline is greater than about 1:1. In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is greater than about 2:1, greater than about 3:1, greater than about 4:1, greater than about 5:1, greater than about 6:1, greater than about 7:1, greater than about 8:1, greater than about 9:1, greater than about 10:1, greater than about 11:1, greater than about 12:1, greater than about 13:1, greater than about 14:1, greater than about 15:1, greater than about 16:1, greater than about 17:1, greater than about 18:1, greater than about 19:1, greater than about 20:1, greater than about 21:1, greater than about 22:1, greater than about 23:1, greater than about 24:1, greater than about 25:1, greater than about 26:1, greater than about 27:1, greater than about 28:1, greater than about 29:1, and greater than about 30:1. In some

embodiments, the molar ratio is greater than about 35:1, greater than about 40:1, greater than about 45:1, and greater than about 50:1.

50 Some compositions provided herein include a tetracycline and divalent or trivalent cation, e.g., metal cation at particular molar ratios of divalent or trivalent cation to tetracycline. For example, some embodiments include compositions comprising a tetracycline and a divalent or trivalent cation, wherein the molar ratio of said divalent or trivalent cation to said tetracycline is greater than about 1:1. In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is greater than about 2:1, greater than about 3:1, greater than about 4:1, greater than about 5:1, greater than about 6:1, greater than about 7:1, greater than about 8:1, greater than about 9:1, greater than about 10:1, greater than about 11:1, greater than about 12:1, greater than about 13:1, greater than about 14:1, greater than about 15:1, greater than about 16:1, greater than about 17:1, greater than about 18:1, greater than about 19:1, greater than about 20:1, greater than about 21:1, greater than about 22:1, greater than about 23:1, greater than about 24:1, greater than about 25:1, greater than about 26:1, greater than about 27:1, greater than about 28:1, greater than about 29:1, and greater than about 30:1. In some

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In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is between about 1:1 to about 30:1, between about 5:1 to about 30:1, between about 10:1 to about 30:1, and between about 20:1 to about 30:1. In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is between about 1:1 to about 50:1, between about 5:1 to about 50:1, between about 10:1 to about 50:1, and between about 20:1 to about 50:1.

In some embodiments, the relative amounts of metal cation present in the compositions of the invention are those amounts which are in excess of the 1:1 metal cation: a tetracycline stoichiometry for each metal cation. In one embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 5:1 to 100:1. In another embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 5:1 to 50:1. In yet another embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 5:1 to 30:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 5:1 to 10:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 10:1 to 20:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 10:1 to 15:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 5:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 10:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 12:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 15:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 20:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 30:1.

Some compositions include carbohydrates in addition to a divalent or trivalent cation. Suitable carbohydrates are those carbohydrates capable of reducing degradation of the tetracycline in at least one solid form prepared in at least one pH environment when compared to a solid form of a tetracycline prepared at the same pH environment lacking suitable carbohydrates. In one embodiment, the pH environment ranges from 3.0 to about 7.0, such as pHs ranging from about 4.0 to about 6.5, from about 5.0 to about 6.5, and from about 5.5 to about 6.5. In one embodiment, at least one solid form is chosen from powders and lyophilized cakes of a tetracycline. In another embodiment of the invention, carbohydrates are those carbohydrates capable of reducing degradation of the tetracycline in solution prepared in at least one pH environment when compared to a solution of a tetracycline prepared at the same pH environment lacking suitable carbohydrates. In one embodiment, the pH environment ranges from 3.0 to about 7.0, such as pHs ranging from about 4.0 to about 6.5, from about 5.0 to about 6.5, and from about 5.5 to about 6.5.

Suitable carbohydrates include mono and disaccharides e.g. an aldose monosaccharide or a disaccharide. Examples of suitable carbohydrates include but are not limited to the anhydrous, hydrated and solvated forms of compounds such as trehalose, lactose, mannose, sucrose and glucose. In one embodiment of the invention, the carbohydrate is a disaccharide. In another embodiment of the invention, the disaccharide is trehalose, lactose or sucrose. In yet another embodiment of the invention, the carbohydrate is lactose, including its different forms such as anhydrous lactose, lactose monohydrate or any other hydrated or solvated form of lactose. In one embodiment of the invention, the carbohydrate is trehalose, including its different forms such as anhydrous trehalose, trehalose dihydrate or any other hydrated or solvated form of trehalose.

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In one embodiment of the invention, the suitable carbohydrate used is lactose monohydrate and the molar ratio of tigeccycline to lactose monohydrate in the lyophilized powder or cake is between 1:0.2 to about 1:5. In another embodiment of the invention, the tigeccycline to lactose monohydrate molar ratio is between 1:1.6 to about 1:3.3.

Some compositions include an antioxidant. Antioxidants can be used to prevent or reduce the oxidation of tetracyclines either in solution or in the solid state. Examples of antioxidants include ascorbic acid, citric acid, trehalose, butylated hydroxyl toluene (BHT), butylated hydroxyl anisole (BHA), sodium metabisulfite, d,l- α -tocopherol, and gentisic acid.

It will be appreciated that the compositions provided herein can include aerosols, liquids, and solids. Solids can include, for example, lyophilized compositions, such as powders, cakes, or the like. Such solids may be water soluble so that they may be used to prepare aqueous solutions. Liquids can include solutions or suspensions, which may be prepared from solid compositions. Liquids include solutions that may be prepared prior to manufacturing procedures such as lyophilization. In one embodiment, the solution may be stored for several hours prior to lyophilization in order to provide greater manufacturing flexibility. Liquids also include solutions that are prepared by reconstitution for use in administration to a patient. Some compositions include solutions made from the lyophilized powder or cake by, for example, reconstitution with saline or other pharmaceutically acceptable diluents. Pharmaceutically acceptable diluents are those listed by USP such as but not limited to water for injection, saline solution, lactated Ringer's solution for injection or dextrose solution. Some compositions include solutions resulting from diluting those reconstituted solutions with pharmaceutically acceptable diluents for use in intravenous bags.

In some embodiments, the pH of a liquid composition provided herein, such as an aqueous solution, is between about pH 2.0 to about pH 8.0, between about pH 2.5 to about pH 7.5. In some embodiments, the pH of the composition is between about pH 3.0 to about pH 7.0, between about pH 3.5 to about pH 6.5, between about pH 4.0 to about pH 6.5, between about pH 4.0 to about pH 6.0, between about pH 4.5 to about pH 6.0, between about pH 4.5 to about pH 5.5, between about pH 5.0 to about pH 5.5, between about pH 5.5 to about pH 6.5, between about pH 3.5 to about pH 4.5. In some embodiments, the pH of the solution is less than pH 7, less than pH 6, less than pH 5, less than pH 4, less than pH 3, and less than pH 2. In some embodiments the pH of the solution is greater than pH 2 and less than pH 7, greater than pH 4 and less than pH 7, greater than pH 4 and less than pH 6, and greater than pH 4 and less than pH 5.

In some embodiments, liquid compositions, such as an aqueous solution, can have an osmolality from about 300 mOsmol/kg to about 500 mOsmol/kg, from about 325 mOsmol/kg to about 450 mOsmol/kg, from about 350 mOsmol/kg to about 425 mOsmol/kg, or from about 350 mOsmol/kg to about 400 mOsmol/kg. In some embodiments, the osmolality of the formulation is greater than about 300 mOsmol/kg, about 325 mOsmol/kg, about 350 mOsmol/kg, about 375 mOsmol/kg, about 400 mOsmol/kg, about 425 mOsmol/kg, about 450 mOsmol/kg, about 475 mOsmol/kg, or about 500 mOsmol/kg. In some embodiments, liquid compositions can have an osmolality from about 200 mOsmol/kg to about 1250 mOsmol/kg. In another embodiment, the osmolality is between about 250 mOsmol/kg and about 1050 mOsmol/kg. In another embodiment, the osmolality is between about 250 mOsmol/kg and about 750 mOsmol/kg. In another embodiment, the osmolality is between about 350 mOsmol/kg and

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about 500 mOsmol/kg. In some embodiments, the osmolality of the solution is less than 500 mOsmol/kg, 450 mOsmol/kg, 400 mOsmol/kg, 350 mOsmol/kg, or 300 mOsmol/kg.

Some embodiments include an aqueous solution comprising a tetracycline having a concentration of at least 1 mg/ml, 5 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 35 mg/ml, 40 mg/ml, 45 mg/ml, or 50 mg/ml.

Some embodiments include an aqueous solution comprising a buffer, such as an acetate buffer (e.g., provided as sodium acetate), wherein the acetate has a concentration of at least 0.01 M, 0.02 M, 0.03 M, 0.04 M, 0.05 M, 0.1 M, 0.15 M, 0.20 M, 0.25 M, 0.30 M, 0.35 M, 0.40 M, 0.45 M, 0.50 M, 0.55 M, 0.60 M, 0.65 M, 0.70 M, 0.75 M, 0.80 M, 0.85 M, 0.90 M, or 0.95 M.

Some embodiments include an aqueous solution comprising a salt comprising divalent or trivalent cation, such as a magnesium salt (e.g., magnesium chloride or magnesium sulfate), having a concentration of at least 0.01 M, 0.02 M, 0.03 M, 0.04 M, 0.05 M, 0.1 M, 0.15 M, 0.20 M, 0.25 M, 0.30 M, 0.35 M, 0.40 M, 0.45 M, 0.50 M, 0.55 M, 0.60 M, 0.65 M, 0.70 M, 0.75 M, 0.80 M, 0.85 M, 0.90 M, or 0.95 M.

In one embodiment, liquid compositions, such as aqueous solutions, have a permeant ion concentration from about 30 mM to about 300 mM. In another embodiment, the permeant ion concentration is between 50 mM and 200 mM. In another embodiment, the permeant ion is selected from the list consisting of chloride and bromide. In another embodiment the permeant ion is chloride. In another embodiment, the permeant ion is bromide.

In some embodiments, aqueous solution compositions comprise a buffer. For example, in some embodiments, the solution comprises acetate. In some embodiments, aqueous solution compositions comprise a base such as NaOH. In some embodiments, aqueous solution compositions comprise an acid such as HCl.

It is contemplated that in some embodiments, reconstituted solutions may be stored in a reconstituted state at room temperature prior to further dilution for injection or topical administration. In some embodiments, storage times at room temperature after reconstitution are much longer than current compositions. In some embodiments, admixing can occur, for example, in an intravenous bag. To prepare an admixture, sufficient reconstituted solution is mixed in an intravenous bag containing a pharmaceutically acceptable diluent such as saline or dextrose solution such as 5 DW.

The concentration of admixtures may easily be determined by those of ordinary skill in the art. The time available for admixture of reconstituted solutions from the compositions may be much longer than those of previously described formulations. Storage times of the admixtures at room temperature may also be much longer than those of the existing compositions. Once admixed, the tetracycline solution is ready for administration by or to the patient. The admixture may be administered alone or together with another pharmaceutical agent or composition.

In some embodiments, the composition does not comprise a pharmaceutically acceptable oil. In some embodiments, an oil can refer to a hydrocarbon compound that is liquid at room temperature and insoluble in water. Examples of pharmaceutically acceptable oils include polyoxyethylene hydrogenated castor oils such as PEG-40 hydrogenated castor oil and PEG-50 hydrogenated castor oil. More examples of pharmaceutically acceptable oils include olive oil, sesame oil, soybean oil, safflower oil, cottonseed oil, corn oil, sunflower oil, arachis oil, coconut oil, an omega-3 polyunsaturated oil, and an omega-3 marine triglyceride.

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In some embodiments, the composition does not comprise a pyridine-containing compound. In one embodiment, the pyridine-containing compound is nicotinamide.

Although some embodiments include gluconate (e.g., as the gluconate salt of a divalent or trivalent metal cation), other embodiments include compositions that do not comprise gluconate.

In some embodiments, the composition does not comprise a non-aqueous tetracycline-solubilizing co-solvent. Such solubilizing co-solvents can include the oil, pyridine-containing compound, and gluconate described above.

Although some embodiments include an antioxidant, other embodiments include compositions that do not comprise an antioxidant (e.g., sodium or magnesium formaldehyde sulfonate; sodium sulfite, metabisulfite or bisulfite; sodium sulfide; alpha-monothioglycerol (also referred to as thioglycerol); and thiosorbitol).

Other various embodiments include compositions that do not include one or more of an alcohol (e.g., a polyhydric alcohol, such as, propylene glycol, ethylene glycol), glycerol, polyethylene glycol, a pyrrolidone-containing compound, a water-miscible local anaesthetic (e.g., procaine, tetracaine), urea, lactose, or a dehydrating agent (e.g., ethyl acetate, acetic anhydride, absolute ethanol, ethyl acetate, acetic anhydride, and mixtures thereof).

Some embodiments include compositions comprising a 7-dimethylamino-tetracycline and a cation. In some such embodiments the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the minocycline is minocycline HCl. In some embodiments the cation comprises Mg^{2+} . In some embodiments, the compositions include a salt selected from $MgCl_2$ (e.g., $MgCl_2 \cdot 6H_2O$), $MgSO_4$ (e.g. $MgSO_4 \cdot 7H_2O$) and magnesium acetate (e.g., $Mg(CH_3COO)_2 \cdot 3H_2O$). In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 10:1, 20:1, 30:1, 40:1, or 50:1. Some embodiments include a buffer. In some such embodiments, the buffer includes NaOH, or sodium acetate (e.g., $NaCH_3COO \cdot 3H_2O$).

Some compositions comprise minocycline and $MgCl_2 \cdot 6H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a base comprising NaOH. Some such embodiments are suitable for intravenous use.

Some compositions comprise minocycline and $MgSO_4 \cdot 7H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising $NaCH_3COO \cdot 3H_2O$ with a pH in the range 4.5-5.5 and an osmolality in the range of about 275-375 mOsm/kg. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH and osmolality of a reconstituted solution can have a pH in the range 4.5-5.5 and an osmolality in the range of about 275-375 mOsm/kg. Some such embodiments are suitable for intravenous use.

Some embodiments comprise minocycline and $Mg(CH_3COO)_2 \cdot 3H_2O$ with a Mg to minocycline molar ratio of about 5:1 with no buffer added. Some such embodiments are suitable for intravenous use.

Some embodiments include minocycline and $MgSO_4 \cdot 7H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a base comprising NaOH with a pH in the range 5.5-6.5. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 5.5-6.5. Some such embodiments are suitable for intravenous use.

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Some embodiments comprise tigecycline and $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising NaOH with a pH in the range 5.5-6.5. Some embodiments comprise tigecycline and $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ with a Mg to minocycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 5.5-6.5. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 5.5-6.5. Some such embodiments are suitable for intravenous use.

Some embodiments comprise tigecycline and $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising NaOH with a pH in the range 5.5-6.5. Some embodiments comprise tigecycline and $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ with a Mg to minocycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 5.5-6.5. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 5.5-6.5. Some such embodiments are suitable for intravenous use.

Some embodiments comprise tigecycline and $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising NaOH with a pH in the range 6.0-7.0. Some embodiments comprise tigecycline and $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ with a Mg to minocycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 6.0-7.0. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 6.0-7.0. Some such embodiments are suitable for topical use. Some such compositions comprise tigecycline with greater than 90%, 95%, or 98% stability for at least 30 days. Some embodiments include compositions comprising an additional constituent such as benzalkonium chloride, a steroid such as hydrocortisone, dexamethasone, thonzonium bromide, tyloxapol, an antiseptic agent such as boric acid, a preservative such as benzalkonium chloride.

Some embodiments comprise tigecycline and $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ with a Ca:minocycline:molar ratio of about 5:1 in a base comprising NaOH with a pH in the range 6.0-7.0. Some embodiments comprise tigecycline and $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ with a Ca to tigecycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 6.0-7.0. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 6.0-7.0. Some such embodiments are suitable for topical use. Some such compositions comprise tigecycline with greater than 90%, 95%, 98% stability for at least 30 days. Some embodiments include compositions comprising an additional constituent such as benzalkonium chloride, a steroid such as hydrocortisone, dexamethasone, thonzonium bromide, tyloxapol, an antiseptic agent such as boric acid, a preservative such as benzalkonium chloride.

Some embodiments include pharmaceutical compositions comprising an aqueous solution of minocycline and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to minocycline is greater than 2:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than about 3:1, greater than about 5:1, greater than about 8:1, greater than about 10:1. In some embodiments, the divalent or trivalent cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In particular embodiments, the divalent or trivalent cation is selected from magnesium,

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calcium, and zinc. In some embodiments, the solution comprises magnesium sulfate and/or magnesium oxide. In particular embodiments, the composition is suitable for intravenous administration.

More embodiments include a pharmaceutical composition comprising an aqueous solution of an 7-dimethylamino-tetracycline antibiotic and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than 3:1 and wherein the solution does not comprise an oil, gluconate, or a pyridine-containing compound, has a pH greater than 2 and less than 7, and is suitable for intravenous administration. In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and glycylcyclines (e.g. tigecycline).

Some embodiments include a water-soluble solid composition, comprising minocycline or a salt thereof and a salt that comprises a divalent or trivalent cation. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than about 1:1, greater than about 2:1, greater than about 3:1, greater than about 5:1, greater than about 8:1, greater than about 10:1. In some embodiments, the salt is selected from magnesium chloride, magnesium bromide, magnesium sulfate, calcium chloride, calcium bromide, calcium sulfate, zinc chloride, gallium chloride, magnesium malate, magnesium gluconate, magnesium citrate, calcium gluconate, calcium citrate, zinc gluconate, zinc acetate, and zinc citrate. In preferred embodiments, the salt is magnesium sulfate. In some embodiments, the composition comprises sodium acetate. In certain embodiments, the composition does not comprise an antioxidant, a pyridine-containing compound (e.g., nicotinamide), or gluconate.

More embodiments include water-soluble solid compositions comprising a 7-dimethylamino-tetracycline antibiotic and a salt comprising a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than 3:1 and wherein the composition does not comprise gluconate or a pyridine-containing compound. In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, glycylcyclines (e.g. tigecycline) and PTK796.

In some embodiments, the water-soluble compositions described above are in the form of a lyophile.

Methods of Preparation

Some embodiments of the present invention include methods for preparing the compositions described herein. Some such methods include combining a tetracycline antibiotic and a divalent or trivalent cation. Some methods further comprise modifying the pH of the compositions. In some methods, modifying the pH comprises adjusting the pH with a pH modifying agent. Examples of pH modifying agents include hydrochloric acid, gentisic acid, lactic acid, citric acid, acetic acid, phosphoric acid, sodium hydroxide, sodium bicarbonate and sodium carbonate. In some embodiments, the pH-modifying agent includes any pharmaceutically acceptable acid, base or buffer capable of adjusting the pH of a tetracycline antibiotic/metal cation solution to between about 3.0 to about 7.0, about 4.0 to about 5.0, about 5.0 to 6.0, about 5.5 to 6.5, about 6.0 to 6.5 or about 4.2 to 4.8. In some embodiments, the acid, base or buffer is used to adjust the pH of a tetracycline antibiotic/metal cation solution to a pH less than 7, 6, 5, or 4. In some embodiments, the acid, base or buffer is used to adjust the pH of a tetracycline antibiotic/metal cation solution to a pH greater than 2 and less than 7, greater than 4 and less than 7, greater than 4 and less than 6, and greater than 4 and less than 5. Examples of such acids include but are not limited to hydrochloric acid, including 1.0 N HCl, gentisic acid, lactic acid, citric acid, acetic acid and phosphoric acid.

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Examples of suitable buffers include as components succinates and acetate. Examples of such bases include but are not limited to aqueous solutions of sodium hydroxide, including 1.0 N NaOH solution, sodium bicarbonate and sodium carbonate.

Compositions of the invention may be prepared via a number of acceptable methods. For example, the metal salts are dissolved in water and the tetracycline antibiotic is added to this solution. Alternatively, the antibiotic is dissolved first and the metal salt is added to the solution. The pH of the solution is then adjusted with an acid, a base or buffer. Other optional agents such as an antioxidant or carbohydrate are then dissolved in the solution. The final solution may be then be used directly in therapy or lyophilized to dryness to form a lyophilized powder or cake for later reconstitution.

In another example, a tetracycline antibiotic may be dry blended with the metal salts and other optional ingredients, and the residual mixture dissolved in water. After the pH of the solution is adjusted, the solution may then be used in therapy or lyophilized to dryness to form a powder or cake.

Lyophilization of solutions described herein may be accomplished by any pharmaceutically acceptable means. Once lyophilized, the compositions of the invention may be stored under an inert gas, such as nitrogen, to further slow the degradation process.

The tetracycline antibiotic used in the various preparation techniques may be any solid-state form of the tetracycline that is sufficiently soluble in water. Such solid-state forms include crystalline tetracycline polymorphs, amorphous forms and salts.

One embodiment for preparing a minocycline-containing pharmaceutical composition includes dissolving minocycline and a salt that comprises a divalent or trivalent cation in water to form a solution and adjusting the pH of the solution to be less than about 7, less than about 6, less than about 5, less than about 4, or less than about 3. In some embodiments, the pH of the solution is adjusted to be greater than about 2 and less than about 7, greater than about 4 and less than about 7, or greater than about 4 and less than about 6. In some embodiments, adjusting the pH comprises adding a base, e.g., NaOH. In some embodiments, adjusting the pH comprises forming a buffer. In some embodiments, forming the buffer comprises adding sodium acetate.

More embodiments for methods of preparing a minocycline-containing pharmaceutical composition includes dissolving minocycline in a solution comprising a divalent or trivalent cation; and adjusting the pH of the solution to be less than 7.

In some embodiments, a solution of a 7-dimethylaminotetracycline can be prepared by adding a 7-dimethylaminotetracycline, an aqueous solution of divalent or trivalent salt to provide a certain divalent or trivalent salt to 7-dimethylaminotetracycline molar ratio. The pH of the solution can be adjusted to a certain pH with a buffer, acid, or a base. The osmolality of the solution can be adjusted to a certain osmolality. The solution can be lyophilized. The lyophilized solution can be reconstituted with a diluent such as water.

In some embodiments, a solution of a 7-dimethylaminotetracycline can be prepared by adding a 7-dimethylaminotetracycline to an acid, such as HCl. The solution can be lyophilized. The lyophilized solution can be reconstituted with a diluent comprising a divalent or trivalent salt to provide a certain divalent or trivalent salt to 7-dimethylaminotetracycline molar ratio. The diluent can further comprise an acid, base, or buffer, such as sodium acetate, to provide a solution of a certain pH.

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In some embodiments, minocycline can be in a buffer comprising MgSO_4 at pH 5. The solution can be lyophilized. The lyophilisate can be reconstituted in an aqueous diluent. In some embodiments, minocycline can be solubilized in an aqueous solution comprising HCl, MgSO_4 and sodium acetate. The solution can be lyophilized. In some embodiments, minocycline can be solubilized in an aqueous solution comprising HCl. The solution can be lyophilized. The lyophilisate can be reconstituted in an aqueous solution. In some embodiments, the reconstituting solution can lack Mg.

Kits

Some embodiments of the present invention include kits comprising a composition described herein. Some kits include a single use container comprising a composition described herein. Single use containers include ampules, vials, and the like. The single-use container can comprise a lyophilized formulation of a composition described herein. Some kits include a diluent for reconstituting the lyophilized formulations of a composition or pharmaceutical composition described herein.

In some embodiments, the compositions of the invention may be prepared for single-dosage use. In this embodiment, the solutions of the invention are lyophilized in individual vials such as 20-mL vials. Upon lyophilization, the vials are stoppered with any acceptable stopper. The stoppered vials are then shipped for use. When needed, the vials can be reconstituted by adding sufficient diluents to achieve the desired concentration of tetracycline. The concentration of reconstituted solutions may be easily determined by those of ordinary skill in the art. Any pharmaceutically acceptable diluent may be used. Examples of such diluents include but are not limited to water, 0.9% saline, Lactated Ringer's injection solution and dextrose solutions including 5% dextrose (5 DW).

In some embodiments, the diluent does not comprise a pharmaceutically acceptable oil (e.g., polyoxyethylene hydrogenated castor oils), a pyridine-containing compound (e.g., nicotinamide), gluconate, an antioxidant, an alcohol (e.g., a polyhydric alcohol, such as, propylene glycol, ethylene glycol), glycerol, polyethylene glycol, a pyrrolidone-containing compound, a water-miscible local anaesthetic (e.g., procaine, tetracaine), urea, lactose, or a dehydrating agent (e.g., ethyl acetate, acetic anhydride, absolute ethanol, ethyl acetate, acetic anhydride, and mixtures thereof). In some embodiments, the diluent does not comprise a tetracycline-solubilizing cosolvent.

In some embodiments, the diluent contains the divalent or trivalent cation. For example, some embodiments include kits that comprise a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises minocycline in an amount such that the molar ratio of the divalent or trivalent cation to minocycline is greater than about 2:1. In some embodiments, the diluent comprises an acid, e.g., HCl. In some embodiments, the diluent comprises a buffer. In some embodiments, the buffer is sodium acetate.

More embodiments include kits comprising a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises a tetracycline antibiotic in an amount such that the molar ratio of the divalent or trivalent cation to tetracycline antibiotic is greater than 3:1.

More embodiments include single use vials comprising any composition wherein the vial comprises an amount of a tetracycline of at least 100 μg , 200 μg , 300 μg , 400 μg , 500 μg ,

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600 µg, 700 µg, 800 µg, 900 µg, 1000 µg. In some embodiments, the vial comprises an amount of a tetracycline of at least 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, and 130 mg. In some embodiments, the vial comprises an amount of a tetracycline of at least 100 mg, 200 mg, 300 mg, 400 mg, and 500 mg. In some embodiments, the vial comprises about 100 mg of a tetracycline. In some embodiments, the tetracycline is minocycline. In some embodiments, the tetracycline is tigecycline. In some such embodiments, a vial can comprise greater than 30 mg and less than 100 mg tigecycline.

Methods of Treatment

Some embodiments include methods of treating or preventing a bacterial infection in a subject by administering a composition described herein. "Treating," as used herein, refers to administering a pharmaceutical composition for therapeutic purposes to a patient suffering from a bacterial infection. "Preventing," as used herein, refers to treating a patient who is not yet infected, but who is susceptible to, or otherwise at risk of, a particular infection, whereby the treatment reduces the likelihood that the patient will develop an infection.

In some embodiments, the administration is via an intravenous route such as by administering an aqueous solution described herein intravenously.

Some such methods include administering an aqueous solution of minocycline and a divalent or trivalent cation to a subject via an intravenous route. Such solutions are described herein.

Some embodiments include administering an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a divalent or trivalent cation to a subject via an intravenous route, wherein the molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than about 3:1 and wherein the solution does not comprise gluconate or a pyridine-containing compound and has a pH greater than 2 and less than 7.

In some embodiments of intravenous administration, the compositions described herein permit use of lower volumes and faster infusion times due to increased concentrations of tetracycline antibiotic and reduced injection site phlebitis as compared to currently available intravenous formulations. In some embodiments, the total volume administered is less than 50 ml, less than 60 ml, less than 70 ml, less than 80 ml, less than 90 ml, less than 100 ml, less than 110 ml, less than 120 ml, less than 130 ml, less than 140 ml, less than 150 ml, less than 200 ml, less than 300 ml, less than 400 ml, less than 500 ml, or less than 1000 ml. In some embodiments, about 100 ml is administered. In some embodiments, the entire volume to be administered is administered in less than 10 minutes, less than 20 minutes, less than 30 minutes, less than 40 minutes, less than 50 minutes, less than 60 minutes, less than 70 minutes, less than 80 minutes, less than 90 minutes, less than 2 hours, less than 3 hours, or less than 4 hours. In some embodiments, the entire volume is administered in 20-70 minutes. In some embodiments, the entire volume is administered in 30-60 minutes.

Some embodiments include administering a composition described herein by a topical route. Examples of topical routes include skin, eye, ear, rectal, vaginal, urethral. Methods of such administration are well known in the art and can include aqueous solution, spray, suppository, salve, or an ointment or the like. Accordingly, some embodiments include administering an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a divalent or trivalent cation to a subject via a topical route. In some such embodiments, the

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molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than about 3:1. In some embodiments, the solution does not comprise gluconate or a pyridine-containing compound. In some embodiments, the solution has a pH greater than 2 and less than 7.

Other embodiments include administering a composition described herein by pulmonary inhalation. For example, compositions may be administered by inhalation of an aerosol of the composition. The aerosol may be formed using dry particles of the composition or by nebulization of a solution of suspension of the composition. Any suitable aerosolization device may be used, including dry-powder inhalers, metered-dose inhalers, and nebulizers.

The following examples illustrate various embodiments of the invention and are not intended to limit the invention in any way.

EXAMPLES

Example 1

Stability at 37° C. for Solutions of Tigecycline or Tygacil® Containing Metal Cations

General procedures: Some of following examples include experiments in which the stabilities of various aqueous solutions of a tetracycline were analyzed. Some solutions included a carbohydrate and/or various molar amounts of metal salts.

The pH of the solutions were adjusted with hydrochloric acid or sodium hydroxide solution. The solutions were incubated at room temperature (approximately 22° C.) or at 37° C. Incubation of solutions at 37° C. was used as a model for long-term storage of solutions.

The stabilities of various aqueous solutions of a tetracycline were analyzed using HPLC. HPLC analyses were conducted on an Agilent 1200: Column: Eclipse Plus C18 4.6×150 mm, 5 µm. Detection: UV at 248 nm. Flow rate: 1.2 mL/min. Tigecycline retention time=4.30 min. Gradient: Solvent A=0.1% trifluoroacetic acid in acetonitrile. Solvent B=0.1% trifluoroacetic acid in water. TABLE 1 shows the HPLC gradient used.

TABLE 1

Time (min)	% Solvent A	% Solvent B
0.0	5	95
9.5	50	50
10.0	5	95
15.0	5	95

A 10 mg/mL Tigecycline aqueous solution was prepared and 300 µL aliquots dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M MgCl₂, 0.1 M CaCl₂ or 0.1 M ZnCl₂ to achieve the desired molar ratio of Tigecycline:metal cation. The tubes were incubated in the dark at 37° C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

A 10 mg/mL (17.08 mol/L) aqueous solution of Tygacil® (Lot D 90293, 53 mg), a commercial Tigecycline formulation containing lactose, was prepared, and 240 µL aliquots were dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M MgCl₂, 0.1 M CaCl₂ or 0.1 M ZnCl₂ to achieve the desired molar ratio of Tigecycline:metal cation. The tubes containing the solu-

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tion were incubated in the dark at 37° C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, and 7 for solutions of Tigecycline at various molar ratios with MgCl₂, CaCl₂, or ZnCl₂ are shown in TABLE 2, TABLE 3, and TABLE 4, respectively. The percentages of Tigecycline remaining at Day 0, 1, 2, 5, and 7 for solutions of Tygacil® at various ratios with MgCl₂, CaCl₂, or ZnCl₂ are shown in TABLE 5, TABLE 6, and TABLE 7, respectively.

TABLE 2

MgCl ₂ :Tigecycline		Day 0	Day 1	Day 2	Day 5	Day 7
Molar ratio						
10:1		99.42	98.93	97.68	92.31	85.95
5:1		99.45	98.85	97.30	88.64	81.41
2:1		99.50	98.57	96.85	84.95	73.95
1:1		99.64	98.64	96.70	82.54	67.87
0.5:1		99.60	98.45	96.52	79.39	62.20
0.2:1		99.56	98.44	95.91	72.81	53.83
0.1:1		99.50	98.29	95.66	67.28	48.68
0:1		99.53	98.23	95.18	58.42	40.90

TABLE 3

CaCl ₂ :Tigecycline		Day 0	Day 1	Day 2	Day 5	Day 7
Molar ratio						
10:1		99.49	99.02	97.89	91.88	86.31
5:1		99.44	98.66	97.31	87.13	80.87
2:1		99.38	98.06	96.66	83.63	75.05
1:1		99.58	98.33	96.54	81.30	70.18
0.5:1		99.56	98.61	96.15	76.00	64.81
0.2:1		99.58	98.47	95.99	72.84	57.19
0.1:1		99.56	98.32	95.66	67.89	49.75
0:1		99.49	98.17	94.98	59.11	39.31

TABLE 4

ZnCl ₂ :Tigecycline		Day 0	Day 1	Day 2	Day 5	Day 7
Molar ratio						
10:1		99.15	99.01	97.82	96.65	95.41
5:1		99.21	98.66	97.76	95.81	92.85
2:1		99.31	98.46	97.32	91.02	85.64
1:1		99.54	98.66	97.59	91.27	82.49
0.5:1		99.53	98.66	97.21	87.15	76.43
0.2:1		99.52	98.38	95.95	79.08	66.83
0.1:1		99.50	98.39	96.11	78.80	64.93
0:1		99.46	98.37	95.02	56.30	39.05

TABLE 5

MgCl ₂ :Tygacil®		Day 0	Day 1	Day 2	Day 5	Day 7
Molar ratio						
10:1		99.61	99.38	98.97	96.51	93.52
5:1		99.47	99.46	98.83	95.38	90.55
2:1		99.49	99.32	98.72	93.20	84.03
1:1		99.63	99.38	98.55	89.21	74.30
0.5:1		99.59	99.28	98.36	86.97	68.84
0.2:1		99.54	99.26	98.43	86.41	64.91
0.1:1		99.48	99.19	98.19	72.43	44.71

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TABLE 6

CaCl ₂ :Tygacil®		Day 0	Day 1	Day 2	Day 5	Day 7
Molar ratio						
10:1		99.41	99.41	98.88	96.51	89.98
5:1		99.40	99.29	98.48	95.38	85.50
2:1		99.45	99.22	98.34	93.20	79.62
1:1		99.71	99.44	98.44	89.21	75.34
0.5:1		99.53	99.16	98.32	86.97	70.45
0.2:1		99.54	99.21	98.30	86.41	63.78
0:1		99.47	99.16	98.16	72.43	42.88

TABLE 7

ZnCl ₂ :Tygacil®		Day 0	Day 1	Day 2	Day 5	Day 7
Molar ratio						
10:1		99.41	99.45	98.90	97.89	95.78
5:1		99.44	99.27	98.68	96.87	94.30
2:1		99.39	99.25	98.74	96.09	92.22
1:1		99.56	99.50	98.98	95.60	90.67
0.5:1		99.48	99.25	98.78	93.73	86.02
0.2:1		99.52	99.35	98.43	89.34	77.79
0:1		99.50	99.27	98.12	69.85	42.15

While Tigecycline decomposed in all tubes over 7 days, the rate of decomposition was significantly lower in solutions containing higher molar ratios of metal cation. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar; however, the rate of Tigecycline decomposition in the presence of zinc was significantly lower. The presence of lactose in the Tygacil® formulation further decreased the rate of decomposition.

Example 2

Stability at Room Temperature for Solutions of Tigecycline or Tygacil® Containing Metal Cations

A 10 mg/mL Tigecycline aqueous solution was prepared and 240 µL aliquots dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M MgCl₂, 0.1 M CaCl₂ or 0.1 M ZnCl₂ to achieve the desired molar ratio of Tigecycline:metal cation. The tubes were incubated in the dark at 37° C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 240 µL aliquots were dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M MgCl₂, 0.1 M CaCl₂ or 0.1 M ZnCl₂ to achieve the desired molar ratio of Tigecycline:metal cation. The tubes were incubated in the dark at 37° C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, 21, 28, and 36 for solutions of Tigecycline at various molar ratios with MgCl₂, CaCl₂, or ZnCl₂ are shown in TABLE 8, TABLE 9, and TABLE 10, respectively. The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, 21, 28, and 36 for solutions of Tygacil® at various ratios with MgCl₂, CaCl₂, or ZnCl₂ are shown in TABLE 11, TABLE 12, and TABLE 13, respectively.

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TABLE 8

MgCl ₂ : Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.58	99.32	99.46	99.03	98.62	95.52	91.90	85.33	76.89
5:1	99.45	99.32	99.41	98.74	98.16	94.04	87.10	76.71	62.60
2:1	99.51	99.27	99.43	98.46	96.97	89.87	76.29	58.07	40.67
1:1	99.66	99.45	99.36	98.35	96.49	85.88	66.59	46.07	31.90
0.5:1	99.64	99.40	99.35	97.76	96.16	81.98	59.70	39.79	28.16
0.2:1	99.56	99.37	99.28	97.93	95.45	75.81	50.38	34.00	24.19
0:1	99.46	99.24	99.15	97.01	94.08	61.98	38.99	24.55	16.33

TABLE 9

CaCl ₂ : Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.58	99.34	99.41	99.05	98.59	95.45	92.00	86.92	82.47
5:1	99.48	99.25	99.27	98.66	98.13	93.61	88.60	81.75	74.95
2:1	99.37	99.27	99.25	98.03	97.16	91.36	82.92	72.83	62.43
1:1	99.57	99.38	99.30	98.53	96.92	89.14	78.35	65.46	53.22
0.5:1	99.59	99.30	99.30	98.32	96.54	86.26	72.73	58.20	45.11
0.2:1	99.48	99.32	99.27	97.94	95.75	80.39	61.83	45.47	26.69
0:1	99.44	99.29	99.17	96.76	93.75	60.72	38.08	23.94	15.72

TABLE 10

ZnCl ₂ : Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.24	98.99	99.49	99.30	99.19	97.49	97.63	96.09	94.32
5:1	99.29	99.13	99.05	99.27	99.16	97.40	95.98	92.80	90.60
2:1	99.34	99.23	99.51	99.06	98.82	95.79	93.63	86.84	80.66
1:1	99.53	99.39	99.47	99.03	98.48	94.61	88.48	79.03	69.44
0.5:1	99.50	99.39	99.33	98.76	96.77	90.07	78.03	65.63	54.07
0.2:1	99.46	99.37	99.33	98.24	96.50	85.72	69.89	55.13	41.97
0:1	99.44	99.39	99.12	97.28	93.31	59.45	37.09	23.57	15.48

TABLE 11

MgCl ₂ : Tygacil ® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.44	99.53	99.34	99.25	99.07	97.30	95.37	92.20	86.32
5:1	99.44	99.61	99.60	99.45	99.32	97.66	95.34	90.98	83.58
2:1	99.48	99.63	99.56	99.43	99.19	96.67	91.94	81.95	66.57
1:1	99.55	99.62	99.61	99.09	99.11	96.50	89.71	74.36	55.95
0.5:1	99.49	99.64	99.60	99.33	98.70	95.10	84.39	64.70	45.04
0.2:1	99.49	99.63	99.57	99.28	98.89	94.03	79.53	57.09	37.94
0:1	99.44	99.57	99.57	99.25	98.78	89.19	65.09	42.56	28.38

TABLE 12

CaCl ₂ : Tygacil ® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.32	99.51	99.45	99.50	99.26	97.41	95.08	92.06	87.88
5:1	99.35	99.51	—	99.33	99.02	97.36	93.42	88.57	82.75
2:1	99.40	99.67	99.46	99.25	98.97	95.76	90.00	81.77	72.75
1:1	99.49	99.60	99.54	99.39	99.02	95.44	88.25	77.42	65.65
0.5:1	99.48	99.60	99.49	99.30	98.55	94.80	85.57	71.96	58.07
0.2:1	99.44	99.57	99.53	99.27	98.89	92.70	80.03	62.28	47.05
0:1	99.45	99.60	99.55	99.18	98.70	88.02	63.58	40.77	28.00

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TABLE 13

ZnCl ₂ : Tygacil ® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	98.91	99.49	99.43	99.46	99.47	98.98	98.68	98.17	98.11
5:1	99.15	99.54	99.51	99.45	99.35	98.88	98.26	97.39	96.15
2:1	99.29	99.57	99.55	99.35	99.37	98.60	97.42	95.30	92.37
1:1	99.44	99.62	99.55	99.61	99.33	97.97	96.29	92.70	87.08
0.5:1	99.47	99.62	99.59	99.48	99.25	97.60	94.10	86.46	76.49
0.2:1	99.45	99.62	99.61	99.47	99.19	96.09	89.52	77.46	63.06
0:1	99.42	99.54	99.52	99.14	98.71	88.25	64.08	41.19	28.09

While Tigecycline decomposed in all tubes over 36 days, the rate of decomposition was significantly lower in solutions containing higher molar ratios of metal cation. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar; however, the rate of Tigecycline decomposition in the presence of zinc was significantly lower. The presence of lactose in the Tygacil® formulation further decreased the rate of decomposition.

Example 3

Stability at 37° C. For Tygacil Solutions Containing High Concentrations of Metal Cations

A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 300 µL aliquots were dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 1 M MgCl₂, 1 M CaCl₂, or 1 M ZnCl₂ to achieve the desired molar ratio of Tigecycline:metal cation. The tubes were incubated in the dark at 37° C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, and 21 for solutions of Tygacil® at various ratios with MgCl₂, CaCl₂, or ZnCl₂ are shown in TABLE 14, TABLE 15, and TABLE 16, respectively.

TABLE 14

MgCl ₂ : Tygacil ® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
30:1	99.64	99.59	99.49	98.54	97.11	89.62	77.13
20:1	99.61	99.56	99.23	97.99	95.94	85.04	63.47
12:1	99.58	99.53	99.14	96.74	94.45	77.71	46.81
5:1	99.68	99.56	99.6	96.06	91.18	59.13	25.95
0:1	99.65	99.23	98.26	75.05	46.66	6.37	1.30

TABLE 15

CaCl ₂ : Tygacil ® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
30:1	99.58	99.55	99.29	97.79	95.9	86.94	69.71
20:1	99.62	99.51	99.18	97.00	93.81	80.6	55.28
12:1	99.60	99.41	98.94	94.94	91.13	69.3	40.59
5:1	99.65	99.42	98.66	92.83	85.72	53.1	24.74
0:1	99.60	99.34	98.25	74.61	45.63	6.26	1.53

TABLE 16

ZnCl ₂ : Tygacil ® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
12:1	99.44	99.27	99.49	98.60	97.66	92.50	83.58
5:1	99.48	—	99.22	97.42	96.21	87.22	71.55
0:1	99.62	—	98.22	73.43	43.3	6.37	1.57

While Tigecycline decomposed in all tubes over 21 days, the rate of decomposition was significantly lower in solutions containing higher molar ratios of metal cation. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar, however, the rate of Tigecycline decomposition in the presence of zinc was significantly lower.

Example 4

Effect of pH on the Stability of Tygacil® Solutions Containing Metal Cations at 37° C.

A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 16504 aliquots were dispensed into four 15 mL polypropylene tubes. The volume of each tube was adjusted to 5500 µL with various dilutions of 0.1 M MgCl₂, 0.1 M CaCl₂, or 0.1 M ZnCl₂, or water (control), to achieve the desired molar ratio of a 1:1 ratio of Tigecycline:metal cation. Sample solutions from each 15 ml tube were taken and adjusted to pH 4, 5, or 6 with 0.1 N or 1 N solutions of NaOH or HCl, taking care to minimize volume changes. Samples solutions were incubated in the dark at 37° C. Samples were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline (expressed as a percentage of the starting concentration) in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions of Tygacil® at 1:1 ratios with MgCl₂, CaCl₂, or ZnCl₂ at various pHs are shown in TABLE 17, TABLE 18, and TABLE 19, respectively. TABLE 20 shows percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions of Tygacil® only at various pHs

TABLE 17

pH for 1:1 MgCl ₂ : Tygacil ®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.51	98.89	98.89	95.72	90.92	54.54
pH 5	99.55	99.09	98.00	84.77	63.60	15.89
pH 6	99.53	98.36	95.79	44.81	23.71	5.19

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TABLE 18

pH for 1:1 CaCl ₂ : Tygacil ®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.49	98.88	98.84	94.43	90.06	55.91
pH 5	99.66	99.02	97.8	81.96	69.23	28.89
pH 6	99.62	98.70	97.87	92.45	87.40	56.79

TABLE 19

pH for 1:1 ZnCl ₂ : Tygacil ®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.47	98.62	99.03	96.14	93.15	73.25
pH 5	99.6	99.21	98.96	93.02	83.48	39.93
pH 6	99.54	99.3	99.16	94.58	86.35	49.21

TABLE 20

pH for Tygacil ®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.48	99.07	98.93	94.28	87.05	44.75
pH 5	99.6	98.94	96.89	49.21	27.49	2.16
pH 6	99.47	95.27	59.56	10.74	2.4	5.22

While Tigecycline decomposed in all tubes over 14 days, the rate of decomposition was significantly lower in solutions with a pH lower than pH 6. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar at pH 4 and 5; however, the rate of Tigecycline decomposition in the presence of magnesium at pH 6 was significantly greater. The rate of Tigecycline decomposition at pH 4 and 5 in solutions containing zinc was lower than solutions containing magnesium or calcium. The rates of Tigecycline decomposition at pH 6, in solutions containing zinc or calcium were similar. The rate of Tigecycline decomposition at all pHs was much lower in the presence of metal cations, especially at higher pH.

Example 5

Effect of pH on the Stability of Tygacil® Solutions
Containing High Concentrations of Metal Cations at
37° C.

A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 1650 µL aliquots were dispensed into four 15 mL polypropylene tubes. The volume of each tube was adjusted to 5500 µL with various dilutions of 1 M MgCl₂, 1 M CaCl₂, or 1 M ZnCl₂, or water (control), to achieve the desired molar ratio of a 1:12 ratio of Tigecycline: metal cation. Sample solutions from each 15 ml tube were taken and adjusted to pH 4, 5, or 6 with 0.1 N or 1 N solutions of NaOH or HCl, taking care to minimize volume changes. Samples solutions were incubated in the dark at 37° C. Samples were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions of Tygacil® at 1:12 ratios with MgCl₂, CaCl₂, or ZnCl₂ at various pHs are shown in TABLE 21, TABLE 22, and TABLE 23, respectively.

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TABLE 21

pH for 12:1 MgCl ₂ : Tygacil ®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.47	98.62	99.18	97.49	95.72	83.14
pH 5	99.61	98.87	99.12	96.53	93.72	69.08
pH 6	99.58	99.26	99.21	95.6	96.96	85.86

TABLE 22

pH for 12:1 CaCl ₂ : Tygacil ®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.48	97.24	98.89	96.01	92.85	73.05
pH 5	99.74	99.36	99.41	97.64	95.94	89
pH 6	99.61	99.44	99.48	98	97.09	92.18

TABLE 23

pH for 12:1 ZnCl ₂ : Tygacil ®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.49	99.29	99.36	98.73	98.35	95.19
pH 5	99.56	99.47	99.47	98.38	98.04	93.38
pH 6	99.65	99.38	99.49	98.78	98.79	97.67

While tigecycline decomposed in all tubes over 14 days, the rate of decomposition was slower in solutions at pH 6. The rates of Tigecycline decomposition in the presence of calcium were slower in solutions at greater pH. When formulated as Tygacil, the rates of tigecycline decomposition in the presence of zinc or magnesium were faster at pH 5.

Example 6

Effect of pH on the Stability of Minocycline
Solutions Containing High Concentrations of MgCl₂
at 37° C.

A 10 mg/mL Minocycline hydrochloride aqueous solution was prepared, and 2500 µL aliquots were dispensed into two 15 mL polypropylene tubes. The volume of each tube was adjusted to 5500 µL with either a dilution of 1 M MgCl₂ to achieve a molar ratio of a 1:10 ratio of Minocycline:metal cation, or water. Sample solutions from each 15 ml tube were taken and adjusted to pH 4, 5, or 6 with 0.1 N or 1 N solutions of NaOH or HCl, taking care to minimize volume changes. Sample solutions were incubated in the dark at 37° C. Samples were taken at various time points and analyzed by HPLC. The fraction of minocycline remaining in each sample was determined.

The percentages of Minocycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions at various pHs of Minocycline at 1:10 ratio with MgCl₂, or Minocycline solutions alone are shown in TABLE 24, and TABLE 25, respectively.

TABLE 24

pH for 10:1 MgCl ₂ : Minocycline	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	98.63	96.97	96.46	94.76	93.43	84.32
pH 5	98.69	97.05	96.19	93.01	89.31	75.42
pH 6	99.03	97.1	96.04	88.45	83.88	76.25

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TABLE 25

pH for Minocycline alone	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	98.75	96.37	96.21	94.99	92.78	81.82
pH 5	98.41	96.72	95.29	85.01	75.14	35.43
pH 6	98.19	95.47	87.55	39.17	14.56	2.2

While Minocycline decomposed in all tubes over 14 days, the rate of decomposition was significantly lower in solutions containing magnesium, especially at higher pH.

Example 7

Stability of Tigecycline Solutions Containing Mixtures of CaCl_2 and MgCl_2 at pH 6 and 37° C.

A 10 mg/mL aqueous solution of Tigecycline was prepared, and 450 μL aliquots were dispensed into 15 mL polypropylene tubes. The volume of each tube was adjusted to 1500 μL with various dilutions of 1 M MgCl_2 and 1 M CaCl_2 , or water (control), to achieve the desired molar ratios of Tigecycline:metal cation. Sample solutions from each 15 mL tube were taken and adjusted to pH 6 with 0.1 N or 1 N solutions of NaOH or HCl, taking care to minimize volume changes. Samples solutions were incubated in the dark at 37° C. Samples were taken at various time points and analyzed by HPLC. The fraction of Tigecycline remaining in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, and 21 for solutions of at various ratios of Tigecycline: MgCl_2 : CaCl_2 at pH 6 are shown in TABLE 26.

TABLE 26

MgCl_2 : CaCl_2 : tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
5:5:1	98.25	98.77	98.23	96.91	92.13	83.64	65.21
5:10:1	98.37	98.23	98.59	97.76	96.10	89.74	79.83
10:5:1	98.17	98.21	98.46	96.59	93.90	80.00	59.39
10:10:1	98.32	98.24	98.50	97.38	95.62	87.14	72.88
5:0:1	98.18	97.93	97.53	90.58	76.71	40.42	12.54
10:0:1	98.16	98.00	98.23	94.91	89.12	62.54	35.75
15:0:1	98.25	98.13	98.21	96.23	92.32	72.15	48.75
20:0:1	98.2	98.08	98.28	96.46	93.72	78.66	57.66
0:5:1	98.11	98.15	98.28	97.19	95.68	89.2	77.2
0:10:1	98.12	98.2	98.55	97.1	96.53	91.74	84.69
0:15:1	98.15	98.21	98.59	97.5	96.93	92.71	86.37
0:20:1	98.28	98.63	98.57	97.4	97.35	93.09	87.45
0:0:1	97.91	88.97	60.59	16.36	7.33	4.14	0

While Tigecycline decomposed in all tubes over 21 days, the rate of decomposition was significantly lower in solutions containing greater relative amounts of calcium cations.

Example 8

Effects of MgCl_2 on Minocycline-Induced Hemolysis in an In Vitro Model of Venous Phlebitis

In vitro hemolysis of rabbit red blood cells (RBCs) after exposure to minocycline formulated in MgCl_2 or CaCl_2 was compared to in vitro hemolysis of RBCs after exposure to minocycline in saline, or exposure to amphotericin B. Minocycline HCl (LKT laboratories) stock solutions were prepared with MgCl_2 in saline, saline, or lactated ringer, and the pH was adjusted with NaOH. Rabbit and sheep red blood

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cells (RBCs) were obtained from Innovative Research laboratory (Michigan, USA). Immediately before use, RBCs were washed three times in 0.9% saline and adjusted to a density of 5% in saline. 200 μL RBCs was added to 800 μL minocycline solution, and mixed by gentle inversion for 2-5 seconds. Samples were incubated at 37° C. or 30 minutes or at 25° C. for 2-5 minutes. Incubated samples were centrifuged at 12000xg for 4 minutes and the supernatants were removed and the hemoglobin absorbance was read at 540 nm. Samples were tested in triplicate. Amphotericin B (MP Biomedicals) and distilled H_2O , or Triton-x and distilled H_2O were used as positive controls; saline was used as a negative control. Percent hemolysis was calculated according to the following formula:

$$\text{Percent hemolysis} = \frac{(\text{absorbance of sample}) - (\text{absorbance of blank})}{\text{Absorbance of Distilled } \text{H}_2\text{O}} \times \frac{100}{\text{Absorbance of Distilled } \text{H}_2\text{O}}$$

In a set of experiments, the pH of minocycline solutions formulated with divalent cations was adjusted to pH 5.85. For RBCs incubated in a minocycline saline solution, hemolysis was in the range of 44%-84% (FIG. 1). For RBCs incubated in a minocycline with Mg^{2+} or Ca^{2+} , hemolysis was approximately 2%. Results summarizing the percent in vitro hemolysis of rabbit RBCs incubated with different formulations of minocycline or amphotericin B at 25° C. are summarized in Table 27.

TABLE 27

Solution	Hemolysis of RBCs in solution relative to water (%)
5 mg/ml minocycline, 10 equiv Mg, pH 5.85	2.8
2.5 mg/ml minocycline, 10 equiv Mg, pH 5.85	3.2
0.5 mg/ml minocycline, 10 equiv Mg, pH 5.85	2.3
5 mg/ml minocycline, 5 equiv Ca, pH 5.85	2.2
2.5 mg/ml minocycline, 5 equiv Ca, pH 5.85	2.94
0.5 mg/ml minocycline, 5 equiv Ca, pH 5.85	2.20
5 mg/ml minocycline, saline, pH 4.17	81.64
2.5 mg/ml minocycline, saline, pH 4.17	84.37
0.5 mg/ml minocycline, saline, pH 4.17	43.82
Amphotericin B	101.31

In another set of experiments, the pH of a minocycline solution formulated with divalent cations was not adjusted and was allowed to fall below the pH of minocycline in saline. For RBCs incubated in a minocycline saline solution, hemolysis was in the range of 44%-84% (FIG. 2). For RBCs incubated in a minocycline with Mg^{2+} or Ca^{2+} , hemolysis was in the range of 0%-5%. Results summarizing the percent in vitro hemolysis of rabbit RBCs incubated with different formulations of minocycline at low pH, or amphotericin B at 25° C. are summarized in Table 28.

TABLE 28

Solution	Hemolysis of RBCs in solution relative to water (%)
5 mg/ml minocycline, 10 equiv Mg, pH 3.5	0.88
2.5 mg/ml minocycline, 10 equiv Mg, pH 3.5	1.12
0.5 mg/ml minocycline, 10 equiv Mg, pH 3.5	2.20
5 mg/ml minocycline, 5 equiv Ca, pH 3.64	—

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TABLE 28-continued

Solution	Hemolysis of RBCs in solution relative to water (%)	
2.5 mg/ml minocycline, 5 equiv Ca, pH 3.64	0.86	5
0.5 mg/ml minocycline, 5 equiv Ca, pH 3.64	4.92	
5 mg/ml minocycline, saline, pH 4.17	81.64	
2.5 mg/ml minocycline, saline, pH 4.17	84.37	10
0.5 mg/ml minocycline, saline, pH 4.17	43.82	
Amphoterin B	101.31	

Hemolysis of RBCs was reduced in an in vitro model of venous phlebitis with minocycline solutions formulated with 15 divalent cations compared to minocycline solutions formulated without divalent cations.

In another set of experiments, hemolysis of rabbit RBCs was measured after exposure to 2.5 mg/ml minocycline formulated with different ratios of divalent cations (MgCl₂, 20 MgSO₄, or CaCl₂). Hemolysis was compared to Minocycline HCl; Triton-x and H₂O were used as positive controls. Results are summarized in Table 29 and shown in FIGS. 4-6.

TABLE 29

2.5 mg/ml minocycline solution		
Cation	Molar ratio cation:minocycline	Hemolysis of RBCs in solution relative to water (%)
MgSO ₄	1:2	22.52
	1:1	24.59
	2:1	40.87
	3:1	25.67
	5:1	2.86
	7:1	1.96
	10:1	0.19
MgCl ₂	1:2	46.91
	1:1	63.77
	2:1	74.87
	3:1	64.62
	5:1	9.43
	7:1	1.57
	10:1	0.35

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TABLE 29-continued

2.5 mg/ml minocycline solution		
Cation	Molar ratio cation:minocycline	Hemolysis of RBCs in solution relative to water (%)
CaCl ₂	1:2	75.22
	1:1	83.89
	2:1	50.84
	3:1	26.58
	5:1	1.16
	7:1	0.75
Minocycline only	10:1	0.40
		37.44
	Triton-x	97.82

FIG. 3 and FIG. 4 show the degree of rabbit RBC hemolysis produced by minocycline formulated in different ratios of MgSO₄ or MgCl₂, respectively, compared to Minocycline only. The data indicates that a 5:1 molar ratio of magnesium to minocycline or greater inhibits the RBC hemolysis observed with minocycline alone. Minocycline (minocin) produced a relative RBC hemolysis of 37%. FIG. 5 shows the degree of rabbit RBC hemolysis produced by minocycline formulated in different ratios of CaCl₂. This data shows that a 25 5:1 molar ratio of calcium to minocycline inhibits the RBC hemolysis observed with minocycline HCl alone.

Overall, these data all suggest that high molar ratios (e.g., a 5:1 molar ratio or greater) of divalent cation (Mg⁺² or Ca⁺²) to minocycline results in significant inhibition of rabbit RBC 30 hemolysis observed with minocycline HCl.

Example 9

Solubility of Minocycline with Divalent Cations

Mixtures were prepared containing minocycline and divalent cations (Mg²⁺ or Ca²⁺) at varying stoichiometry and pH. The solubility of minocycline was assessed according to the turbidity of the mixture at 0 hr, 24 hr, 48 hr, 72 hr, 96 hr, 120 40 hr, 144 hr, and 168 hr. A clear solution denoted complete solubility. Table 30 summarizes data for minocycline with Mg²⁺ at 0 hr and 24 hr. Table 31 summarizes data for minocycline with Ca²⁺ at 0 hr and 24 hr.

TABLE 30

		Molar ratio cation (Mg ²⁺):Minocycline															
		0		1:2		1:1		2:1		3:1		5:1		7:1		10:1	
Time (hr)		0	24	0	24	0	24	0	24	0	24	0	24	0	24	0	24
1 mg/ml minocycline	pH 4	○	○									○	○	○	○	○	○
	pH 5	○	○									○	○	○	○	○	○
	pH 6	○	○									○	○	○	○	○	○
	pH 7	○	○									○	○	○	○	○	○
5 mg/ml minocycline	pH 4	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 6	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●
10 mg/ml minocycline	pH 4	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 6	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●
20 mg/ml minocycline	pH 4	○	●									○	○	○	○	○	○
	pH 5	○	○									○	●	○	●	○	●
30 mg/ml minocycline	pH 4	○	●									○	○	○	○	○	○
	pH 5	○	●									○	●	○	●	○	●

●: insoluble;

○: soluble

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TABLE 31

		Molar ratio cation (Ca ²⁺):minocycline															
		0		1:2		1:1		2:1		3:1		5:1		7:1		10:1	
		0	24	0	24	0	24	0	24	0	24	0	24	0	24	0	24
1 mg/ml minocycline	pH 4	○	○									○	○	○	○	○	○
	pH 5	○	○									○	○	○	○	○	○
	pH 6	○	○									○	○	○	○	○	○
	pH 7	○	○									○	●	○	●	○	●
5 mg/ml minocycline	pH 4	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 6	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○
10 mg/ml minocycline	pH 4	○	○	○	○	○	○										
	pH 5	○	○	○	○	○	○										
	pH 6	○	○	○	○	○	○										
20 mg/ml minocycline	pH 4	○	●									○	○	○	○	○	○
	pH 5	○	○									○	○	○	○	○	○
30 mg/ml minocycline	pH 4	○	●									○	●	○	●	○	●
	pH 5	○	●									○	○	○	○	○	○

●: insoluble;
○: soluble

The data demonstrates that minocycline stays in solution upon introduction of a cation at concentrations of 10 mg/ml and less if the pH is less than 5. At higher pH, introduction of a cation initially reduces solubility. For example, a 5 mg/ml minocycline solution at pH 6 becomes insoluble on addition of Mg²⁺. Surprisingly, at a molar ratio of cation:minocycline of 5:1 or more, the minocycline of such solutions becomes soluble, suggesting that high ratios of cation increases the solubility of minocycline.

Table 32 summarizes data for minocycline with Mg²⁺ at 48 hr and 72 hr.

TABLE 32

		Molar ratio cation (Mg ²⁺):minocycline															
		0		1:2		1:1		2:1		3:1		5:1		7:1		10:1	
		48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72
1 mg/ml minocycline	pH 4	○	○									○	○	○	○	○	○
	pH 5	○	○									○	○	○	○	○	○
	pH 6	○	○									○	○	○	○	○	○
	pH 7	○	○									○	○	○	○	○	○
5 mg/ml minocycline	pH 4	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○
	pH 6	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●
10 mg/ml minocycline	pH 4	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	●	●	○	●	●	●	●	●	●	●	○	●	○	●	○	○
	pH 6	●	●	●	●	●	●	●	●	●	●	○	●	●	●	●	●
20 mg/ml minocycline	pH 4	●	●									○	○	○	○	○	○
	pH 5	●	●									●	●	●	●	●	●
30 mg/ml minocycline	pH 4	●	●									○	○	○	○	○	○
	pH 5	●	●									●	●	●	●	●	●

●: insoluble;
○: soluble

TABLE 33

Salt	Formulation stored at 37° C.	Stability of tigecycline (%)					
		0 day	1 day	2 days	5 days	7 days	14 days
MgCl ₂	12 eq 20 mg/mL	97.97	97.43	96.37	92.63	88.41	
	5 eq 20 mg/mL	98.09	97.38	96.42	88.64	81.62	

Example 10

Long-Term Stability of Tigecycline at Various Temperatures

Table 33, Table 34, and Table 35 show percentage remaining tigecycline for different formulations of tigecycline at pH 6, stored at 37° C., room temperature, and 4° C., respectively. Formulations of tigecycline comprising increasing concentrations of tigecycline and increasing concentrations of CaCl₂ showed increased stability.

TABLE 33-continued

Salt	Formulation stored at 37° C.	Stability of tigecycline (%)					
		0 day	1 day	2 days	5 days	7 days	14 days
	2 eq 20 mg/mL	97.95	97.28	94.1	80.59	69.88	
	12 eq 3 mg/mL	98.17	98.05	97.08	93.78	88.16	

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TABLE 33-continued

Salt	Formulation stored at 37° C.	Stability of tigecycline (%)						
		0 day	1 day	2 days	5 days	7 days	14 days	
CaCl ₂	5 eq 3 mg/mL	98.3	97.72	96.77	86.97	73.76		5
	2 eq 3 mg/mL	98.21	97.22	93.75	62.21	45.31		
	12 eq 20 mg/mL	98.3	98	97.63	96.1	95.24	91.44	10
	5 eq 20 mg/mL	98.16	97.75	97.4	95.82	94.81	89.26	
	2 eq 20 mg/mL	98.25	97.85	97.22	95.28	93.64	88.61	
	12 eq 3 mg/mL	98.29	98.03	97.74	96.79	95.92	91.07	15
ZnCl ₂	5 eq 3 mg/mL	98.21	97.96	97.32	95.37	94.42	86.36	
	2 eq 3 mg/mL	98.17	97.74	96.57	92.99	90.22		
	1 eq 20 mg/mL	98.26	97.19	93.86	81.02	72.41		20
	1 eq 3 mg/mL	98.29	97.88	96.73	86.5	74.32		

TABLE 34

Salt	Formulation stored at room temperature	Stability of tigecycline (%)						
		0 day	7 days	14 days	28 days	42 days	58 days	
MgCl ₂	12 eq 20 mg/mL	97.97	96.56	93.4	79.44			
	5 eq 20 mg/mL	98.09	94.2	82.17				
	2 eq 20 mg/mL	97.95	87.57	67.91				
	12 eq 3 mg/mL	98.17	97.22	94.91	80.14			
	5 eq 3 mg/mL	98.3	96.45	89.91				
	2 eq 3 mg/mL	98.21	92.66	66.91				
CaCl ₂	12 eq 20 mg/mL	98.3	97.91	97.36	95.69	95.32	93.02	
	5 eq 20 mg/mL	98.16	97.88	97.23	95.24	94.08	90.78	45
	2 eq 20 mg/mL	98.25	97.97	97.08	94.42	93.08	87.95	
	12 eq 3 mg/mL	98.29	98.01	97.7	96.37	95.78	93.67	
	5 eq 3 mg/mL	98.21	97.84	97.29	95.39	94.22	90.37	50
	2 eq 3 mg/mL	98.17	97.53	96.47	92.85	90.07	79.52	
ZnCl ₂	1 eq 20 mg/mL	98.26	82.44	65.73				
	1 eq 3 mg/mL	98.29	97.11	93.1				

TABLE 35

Salt	Formulation stored at 4° C.	Stability of tigecycline (%)					
		0 day	14 day	28 days	35 days	58 days	162 days
MgCl ₂	12 eq 20 mg/mL	97.97	97.68	96.16	95.36	89.95	

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TABLE 35-continued

Salt	Formulation stored at 4° C.	Stability of tigecycline (%)					
		0 day	14 day	28 days	35 days	58 days	162 days
CaCl ₂	5 eq 20 mg/mL	98.09	96.22	78.05	69.76		
	2 eq 20 mg/mL	97.95	91.23	54.38	43.33		
	12 eq 3 mg/mL	98.17	97.76	95.76	94.19	80.31	
	5 eq 3 mg/mL	98.3	97.48	91.75	86.21		
	2 eq 3 mg/mL	98.21	96.23	84.6	76.81		
	12 eq 20 mg/mL	98.3	98.28	97.78	97.61	97.87	96.4
ZnCl ₂	5 eq 20 mg/mL	98.16	97.97	97.65	97.79	97.78	95.22
	2 eq 20 mg/mL	98.25	98.08	97.69	97.8	97.75	94.9
	12 eq 3 mg/mL	98.29	98.37	98.16	97.79	98.15	97.27
	5 eq 3 mg/mL	98.21	98.17	97.97	97.76	97.99	96.75
	2 eq 3 mg/mL	98.17	98.14	97.45	97.53	97.56	93.35
	1 eq 20 mg/mL	98.26	77.12	53.06	45.63		
	1 eq 3 mg/mL	98.29	97.73	96.38	95.02	88.53	

Example 11

Solubility of Tetracycline Formulations

The solubility of four non-dimethylamino tetracyclines, with and without Mg²⁺, was examined. The results are summarized in Table 36.

TABLE 36

		Molar ratio cation (Mg ²⁺):antibiotic							
		0	0.5:1	1:1	2:1	3:1	5:1	7:1	10:1
10 mg/ml tetracycline	pH 4	•	•	•	•	•	•	•	•
	pH 5	•	•	•	•	•	•	•	•
	pH 6	•	•	•	•	•	•	•	•
10 mg/ml chlortetracycline	pH 4	•					○	○	○
	pH 5	•					•	•	•
	pH 6	•					•	•	•
10 mg/ml doxycycline	pH 4	○					•	•	•
	pH 5	○					•	•	•
	pH 6						○ [#]	○ [#]	○ [#]
10 mg/ml oxytetracycline	pH 4	•					•	•	•
	pH 5	•					•	○	○
	pH 6	•					•	○	○

●: insoluble;

○: soluble;

[#]fell out of solution after 24 hrs at room temperature

A comparison with the results for minocycline described in Example 9 indicates that non-dimethylamino-tetracyclines, such as tetracycline, chlortetracycline, doxycycline, and oxytetracycline have solubility characteristics that differ from dimethylamino-tetracyclines. For example, as summarized in Table 36, tetracycline remains insoluble at various pH and amounts of a divalent cation such as Mg²⁺. Chlortetracycline becomes soluble with increasing concentrations of a divalent cation, but remains insoluble in the absence of any divalent cation, such as Mg²⁺. Doxycycline is soluble in the

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absence of divalent cations, such as Mg^{2+} , but is insoluble in the presence of divalent cations at low pH. Similarly, oxytetracycline remains insoluble in the presence of divalent cations, such as Mg^{2+} , at low pH.

Example 12

Study of the Effect of Mg^{2+} on the Uptake of
Minocycline in Human Umbilical Vein Endothelial
Cells (HUVEC)

Cells and reagents: Human umbilical vein endothelial cells (HUVEC) were purchased from Lonza and maintained according to manufacturer's recommendations in EGM-2 media. A 10 mg/mL solution of minocycline was prepared in 13.6 mg/mL Na-acetate without addition of Mg. This stock solution was further diluted in saline to 1 mg/mL with addition of Mg in the form of 1 M $MgSO_4$ to generate the following molar ratios of Mg to minocycline: 0, 1, 2.5, 5, 10, 25.

Uptake experimental conditions: HUVECs were seeded at 4.5×10^5 cells/well density in 6-well plates in EGM-2 media. Two days after seeding, cells were washed once with 2 mL of saline, and then 2 mL of 1 mg/mL drug solution in saline prepared as described above was placed in each well in triplicate. Plates were incubated in a CO_2 incubator at 37° C. for 30 min. Drug solutions were aspirated and cells were washed once with 2 mL of saline. 0.5 mL of saline was placed in each well and the cell monolayer was scraped using a plastic cell scraper. Cell suspensions were transferred to 1.5 mL plastic tubes and sonicated for 30 sec at maximal power. Cell lysates were spun down for 10 min on a table top microcentrifuge at maximum speed and supernatants were collected. Several wells of HUVEC cells were treated with saline only and processed the same way as drug-treated cells to generate mock cell lysate which was used below for calibration curve preparation.

Sample preparation for LCMS analysis: To prepare a calibration curve, 1 mg/mL minocycline solution in water was diluted in mock cell lysate to produce 100 μ L of standards with the following concentrations: 10, 5, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.02, 0.01 μ g/mL.

50 μ L of supernatants from drug-treated samples or standards were mixed with 200 μ L of 1% trifluoroacetic acid in acetonitrile containing 1 μ g/mL of gatifloxacin, vortexed and centrifuged at 3000 g for 30 min at RT. 150 μ L of supernatants was removed and mixed with 450 μ L of water. After vortexing, the mixture was centrifuged at 3000 g for 5 min at RT. Supernatants were collected and subjected to LCMS analysis to determine minocycline concentration.

Data processing: Uptake data were presented as percentage relative to the sample with no Mg present, which was considered as 100%.

Uptake of minocycline at 1 mg/mL in saline with various Mg/minocycline ratios was tested in HUVEC with an incubation time was 30 min. The results are summarized in FIG. 6 and FIG. 7. FIGS. 6 and 7 demonstrate that a decrease in intracellular uptake of minocycline is observed as the concentration of a divalent cation, such as Mg^{2+} increases. While not being bound by any particular theory, this result suggests that the mechanism for the reduction in hemolysis observed in the minocycline/cation formulations described herein may be attributed to reduced RBC uptake.

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Example 13

Preparing Certain Formulations of
Dimethylamino-Tetracyclines

Formulation 1

A formulation comprising minocycline with $MgCl_2$ and NaOH suitable for intravenous administration is prepared. 100 mg minocycline is added to a 10 ml aqueous solution of $MgCl_2 \cdot 6H_2O$ to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/mL minocycline solution. The pH of the mixture is adjusted by adding NaOH to a pH in the range of pH 4.5-pH 5.5. A single attempt of lyophilization resulted in a non-flocculent solid.

Formulation 2

A formulation comprising minocycline with $MgSO_4$ and sodium acetate suitable for intravenous administration is prepared. 100 mg minocycline is added to an aqueous solution of $MgSO_4 \cdot 7H_2O$ to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/mL minocycline solution. The pH of the solution is adjusted by adding sodium acetate to a pH in the range of pH 4.5-pH 5.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 4.5-pH 5.5 and an osmolality in the range of 275 mOsm/kg-375 mOsm/kg.

Formulation 3

A formulation comprising minocycline with $Mg(C_2H_3O_2)_2$ suitable for intravenous administration is prepared. 100 mg minocycline is added to an aqueous solution of $Mg(C_2H_3O_2)_2 \cdot 3H_2O$ to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/mL minocycline solution. The solution is then lyophilized to dryness.

Formulation 4

A formulation comprising minocycline with $MgSO_4$ and NaOH suitable for intravenous administration is prepared. 100 mg minocycline is added to an aqueous solution of $MgSO_4 \cdot 7H_2O$ to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/mL minocycline solution. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 4.5-pH 5.5. The solution is lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 4.5-pH 5.5 and an osmolality in the range of 150 mOsm/kg-250 mOsm/kg.

Formulation 5

A formulation comprising tigecycline with $MgSO_4$ and NaOH suitable for intravenous administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of $MgSO_4 \cdot 7H_2O$ to provide a cation to tigecycline molar ratio of 5:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5-pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5-pH 6.5.

Formulation 6

A formulation comprising tigecycline with $MgSO_4$ and NaOH suitable for intravenous administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of $MgSO_4 \cdot 7H_2O$ to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5-pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5-pH 6.5.

Formulation 7

A formulation comprising tigecycline with $MgCl_2$ and NaOH suitable for intravenous administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of

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MgCl₂·6H₂O to provide a cation to tigecycline molar ratio of 5:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5-pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5-pH 6.5.

Formulation 8

A formulation comprising tigecycline with MgCl₂ and NaOH suitable for intravenous administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of MgCl₂·6H₂O to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5-pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5-pH 6.5.

Formulation 9

A formulation comprising tigecycline with MgSO₄ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of MgSO₄·7H₂O to provide a cation to tigecycline molar ratio of 5:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0-pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0-pH 7.0.

Formulation 10

A formulation comprising tigecycline with MgSO₄ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of MgSO₄·7H₂O to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0-pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0-pH 7.0.

Formulation 11

A formulation comprising tigecycline with CaCl₂ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of CaCl₂·6H₂O to provide a cation to tigecycline molar ratio of 5:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0-pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0-pH 7.0.

Formulation 12

A formulation comprising tigecycline with CaCl₂ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of CaCl₂·6H₂O to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0-pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0-pH 7.0.

Example 14

Minocycline Kits

Kit 1

A kit is prepared comprising two vials. The first vial is prepared by dissolving 108 mg minocycline HCl in an acidic solution. The solution is lyophilized to dryness. The second vial contains 10 ml diluent that includes 26.9 mg/ml MgSO₄·7H₂O and 13.6 mg/mL Na(C₂H₃O₂)₂·3H₂O. The lyophile is then reconstituted with the diluent prior to use.

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Kit 2

A kit is prepared comprising two vials. The first vial is prepared by dissolving 108 mg minocycline HCl in an acidic solution. The solution is lyophilized to dryness. The second vial contains 10 ml diluent that includes 26.9 mg/ml MgSO₄·7H₂O and enough NaOH to adjust the pH to approximately 5. The lyophile is then reconstituted with the diluent prior to use.

All references cited herein, including but not limited to published and unpublished applications, patents, and literature references, are incorporated herein by reference in their entirety and are hereby made a part of this specification. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material. The term "comprising" as used herein is synonymous with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth herein are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of any claims in any application claiming priority to the present application, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

The above description discloses several methods and materials of the present invention. This invention is susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this disclosure or practice of the invention disclosed herein. Consequently, it is not intended that this invention be limited to the specific embodiments disclosed herein, but that it cover all modifications and alternatives coming within the true scope and spirit of the invention.

What is claimed is:

1. A method of treating a bacterial infection in a subject, wherein the method consists of:
administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration,
wherein the composition consists of an aqueous solution consisting of minocycline or a salt thereof, a salt that comprises a magnesium cation, and a base,
wherein the molar ratio of magnesium cation to minocycline is greater than about 4:1, and
wherein the composition has a pH that is no less than 4 and no greater than 6,
whereby injection site hemolysis of red blood cells is reduced relative to intravenous administration of a composition that does not include magnesium.
2. The method of claim 1, wherein the concentration of minocycline in the composition is at least 0.1 mg/ml.
3. The method of claim 1, wherein the concentration of minocycline in the composition is at least 1 mg/ml.
4. The method of claim 1, wherein the concentration of minocycline in the composition is at least 5 mg/ml.
5. The method of claim 1, wherein the concentration of minocycline in the composition is at least 10 mg/ml.
6. The method of claim 1, wherein the composition has a pH between about 4.5 to about 6.

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7. The method of claim 1, wherein the composition has a pH between about 4.5 to about 5.5.

8. The method of claim 1, wherein the molar ratio of magnesium cation to minocycline is greater than or equal to 5:1.

9. The method of claim 1, wherein the molar ratio of magnesium cation to minocycline is from 5:1 to 10:1.

10. The method of claim 1, wherein the osmolality of the solution is less than 500 mOsm/kg.

11. The method of claim 1, wherein the osmolality of the solution is less than 400 mOsm/kg.

12. The method of claim 1, wherein the osmolality of the solution is less than 350 mOsm/kg.

13. The method of claim 1, wherein the salt that comprises a magnesium cation is magnesium sulfate.

14. The method of claim 1, wherein the salt that comprises a magnesium cation is magnesium acetate.

15. The method of claim 1, wherein the salt that comprises a magnesium cation is magnesium chloride.

16. The method of claim 1, wherein the base is NaOH.

17. The method of claim 1, wherein the total volume of the composition administered is less than 1000 ml.

18. The method of claim 1, wherein the total volume of the composition administered is less than 500 ml.

19. The method of claim 1, wherein the total volume of the composition administered is less than 200 ml.

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20. The method of claim 1, wherein the total volume of the composition administered is less than 110 ml.

21. The method of claim 1, wherein the composition is administered in less than 60 minutes.

22. The method of claim 1, wherein the composition is administered in less than 40 minutes.

23. The method of claim 1, wherein the composition is administered in less than 20 minutes.

24. The method of claim 1, wherein the amount of minocycline in the composition is at least 80 mg.

25. The method of claim 1, wherein the amount of minocycline in the composition is at least 100 mg.

26. The method of claim 1, wherein the amount of minocycline in the composition is about 100 mg.

27. The method of claim 1, wherein the amount of minocycline in the composition is at least 130 mg.

28. The method of claim 1, wherein the amount of minocycline in the composition is at least 200 mg.

29. The method of claim 1, wherein the amount of minocycline in the composition is at least 300 mg.

30. The method of claim 1, wherein the amount of minocycline in the composition is at least 400 mg.

31. The method of claim 1, wherein the amount of minocycline in the composition is at least 500 mg.

* * * * *

(12) **United States Patent**
Griffith et al.

(10) **Patent No.:** **US 9,278,105 B2**
(45) **Date of Patent:** ***Mar. 8, 2016**

(54) **TETRACYCLINE COMPOSITIONS**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to compositions, pharmaceutical compositions, and methods for preparing the same, comprising a tetracycline with improved stability and solubility. Some embodiments include a tetracycline with an excess of a divalent or trivalent cation.

60 Claims, 7 Drawing Sheets

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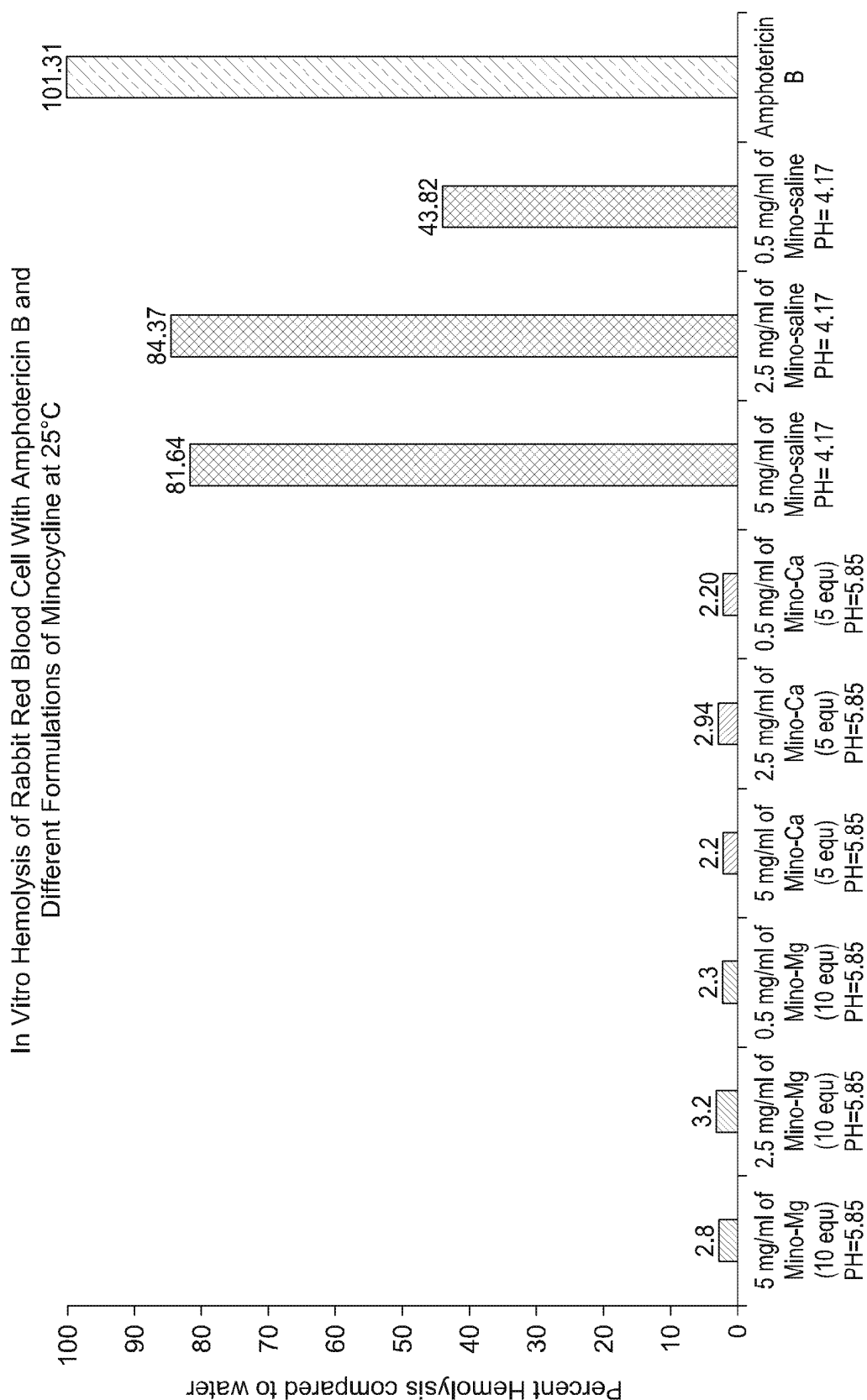


FIG. 1

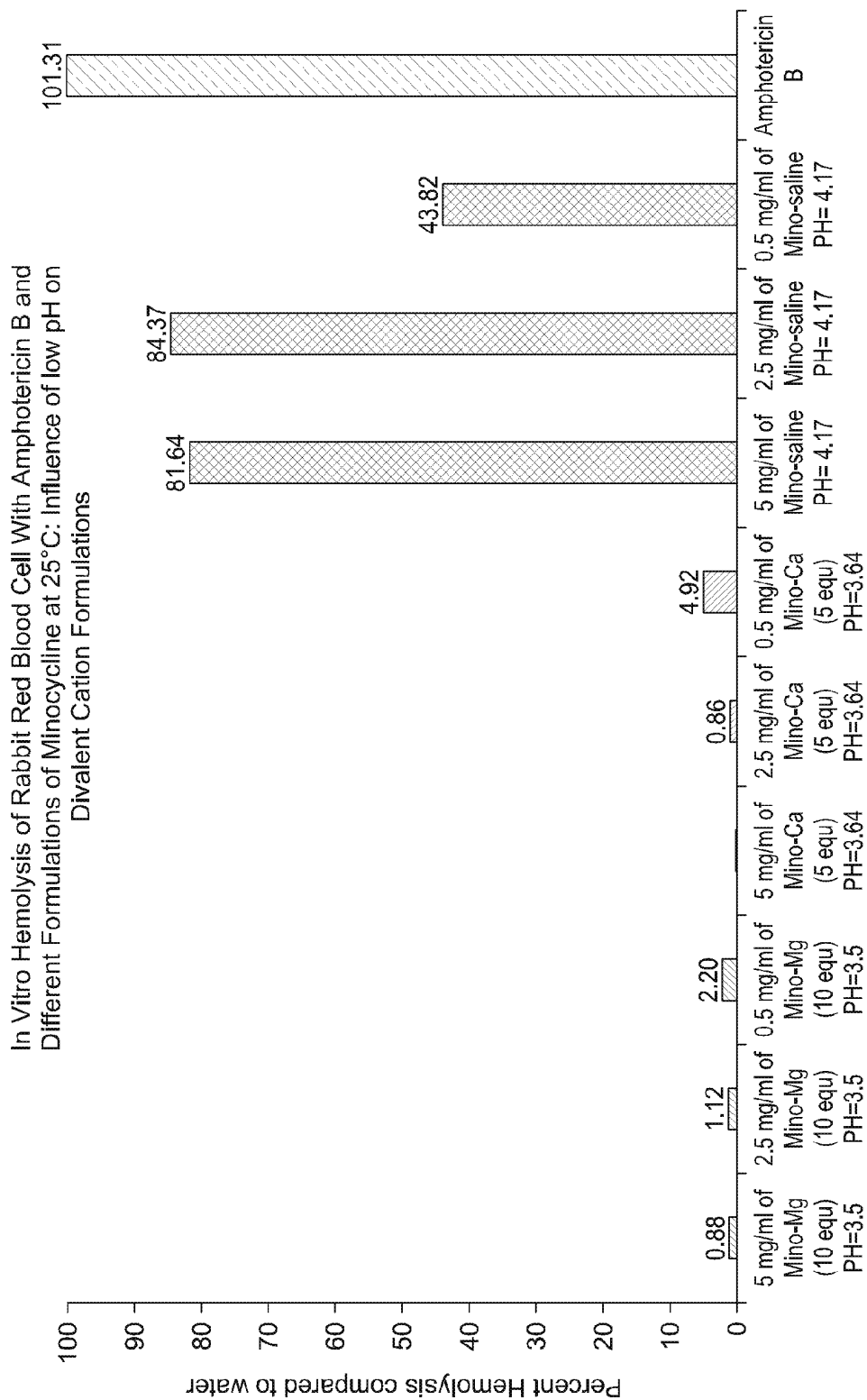


FIG. 2

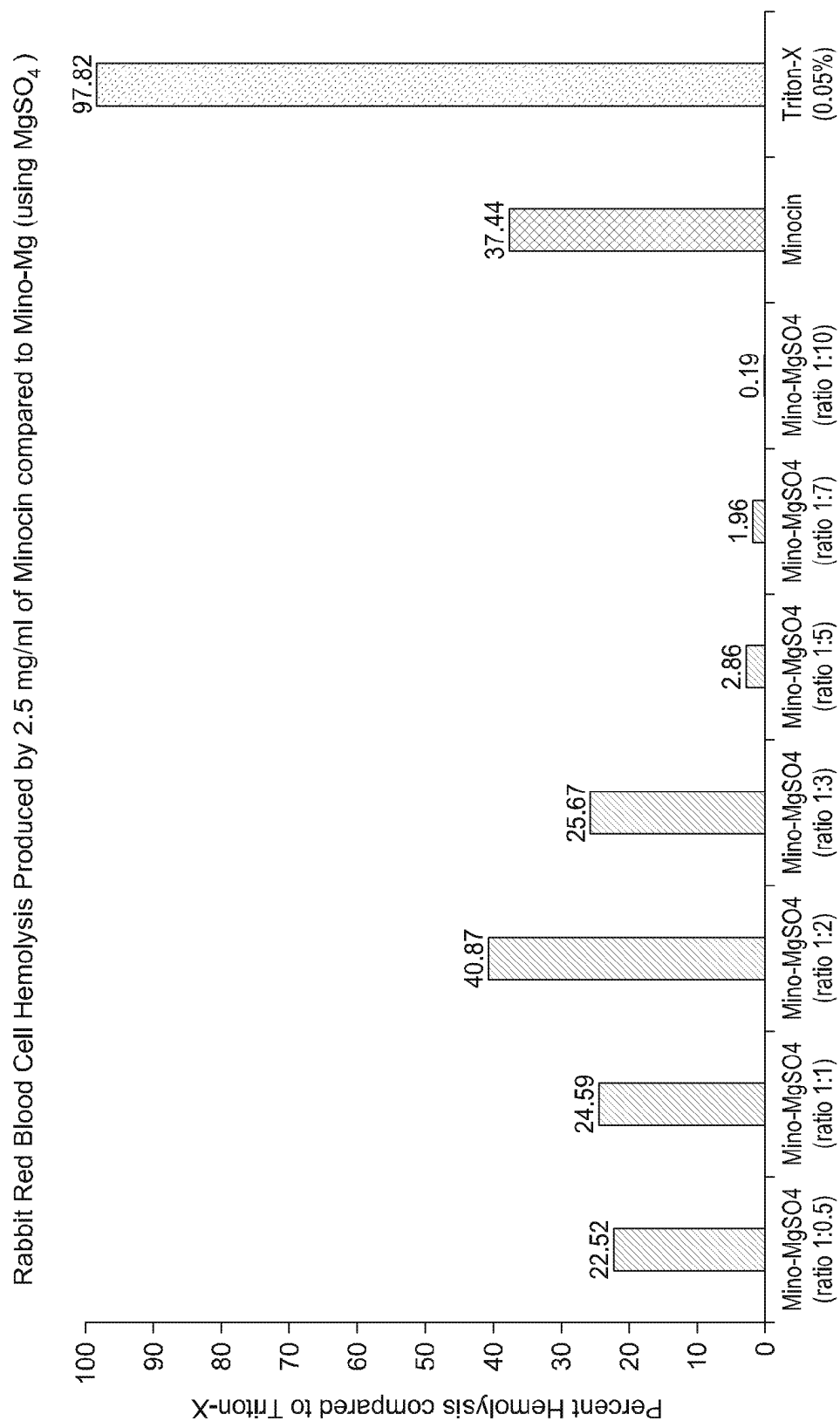


FIG. 3

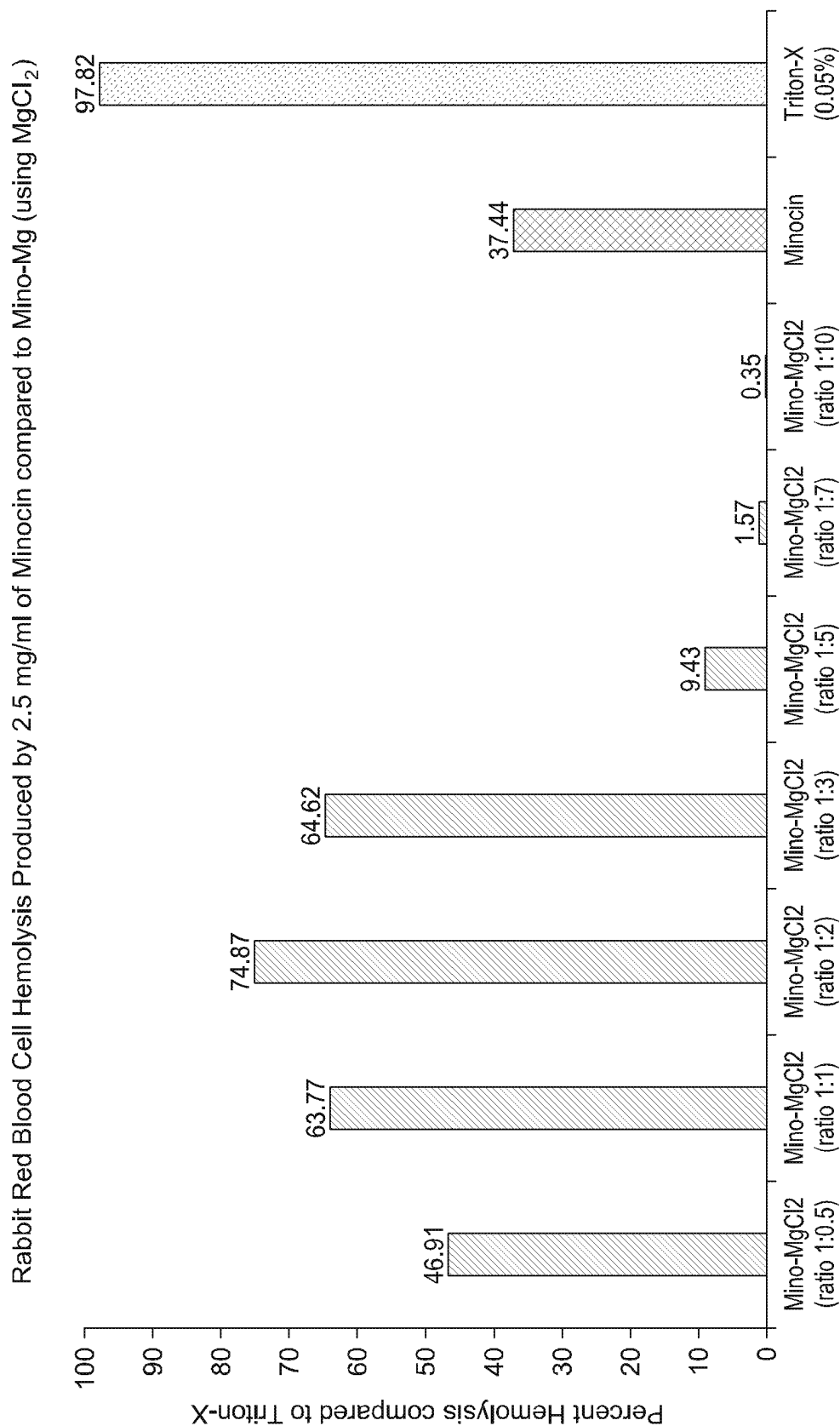


FIG. 4

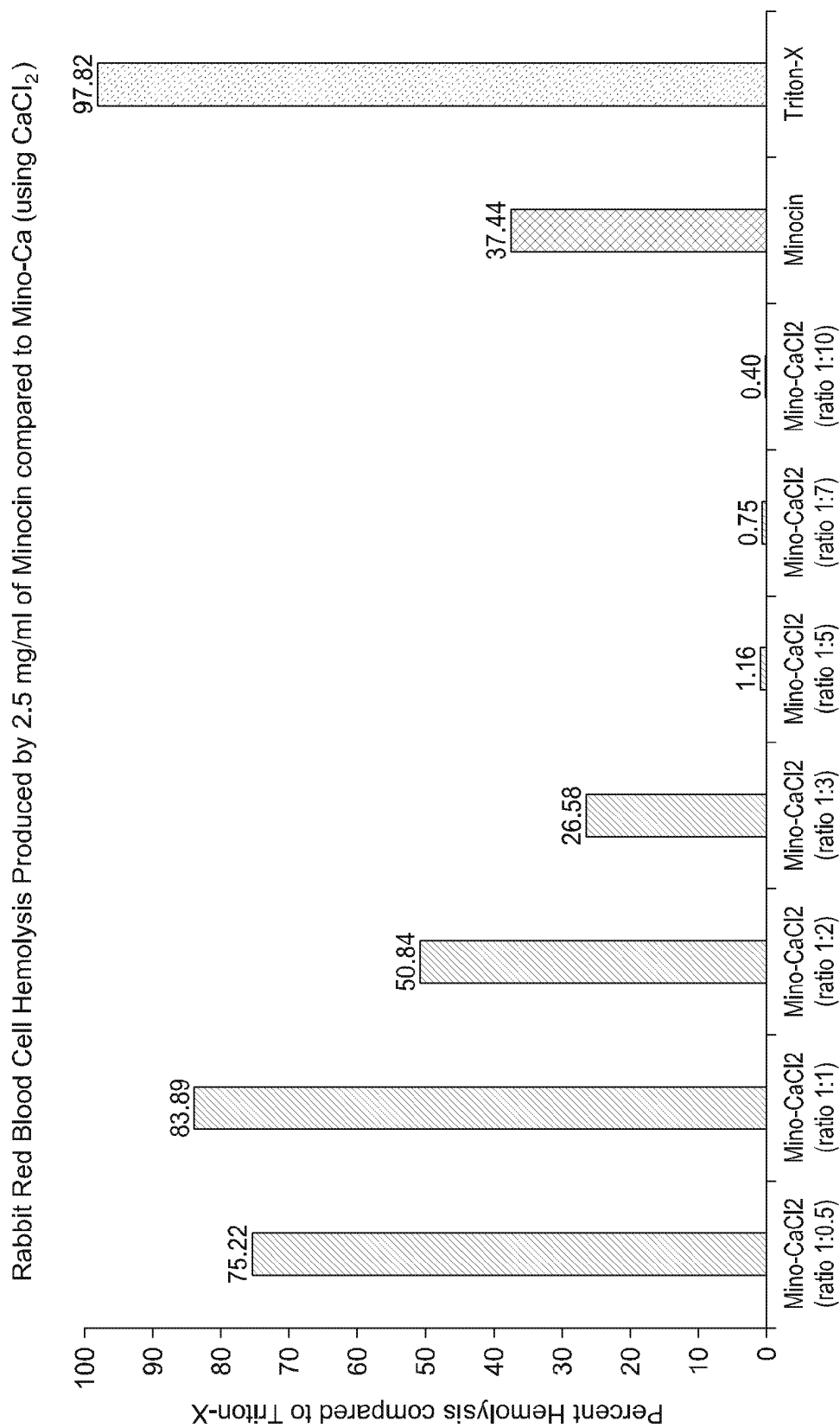


FIG. 5

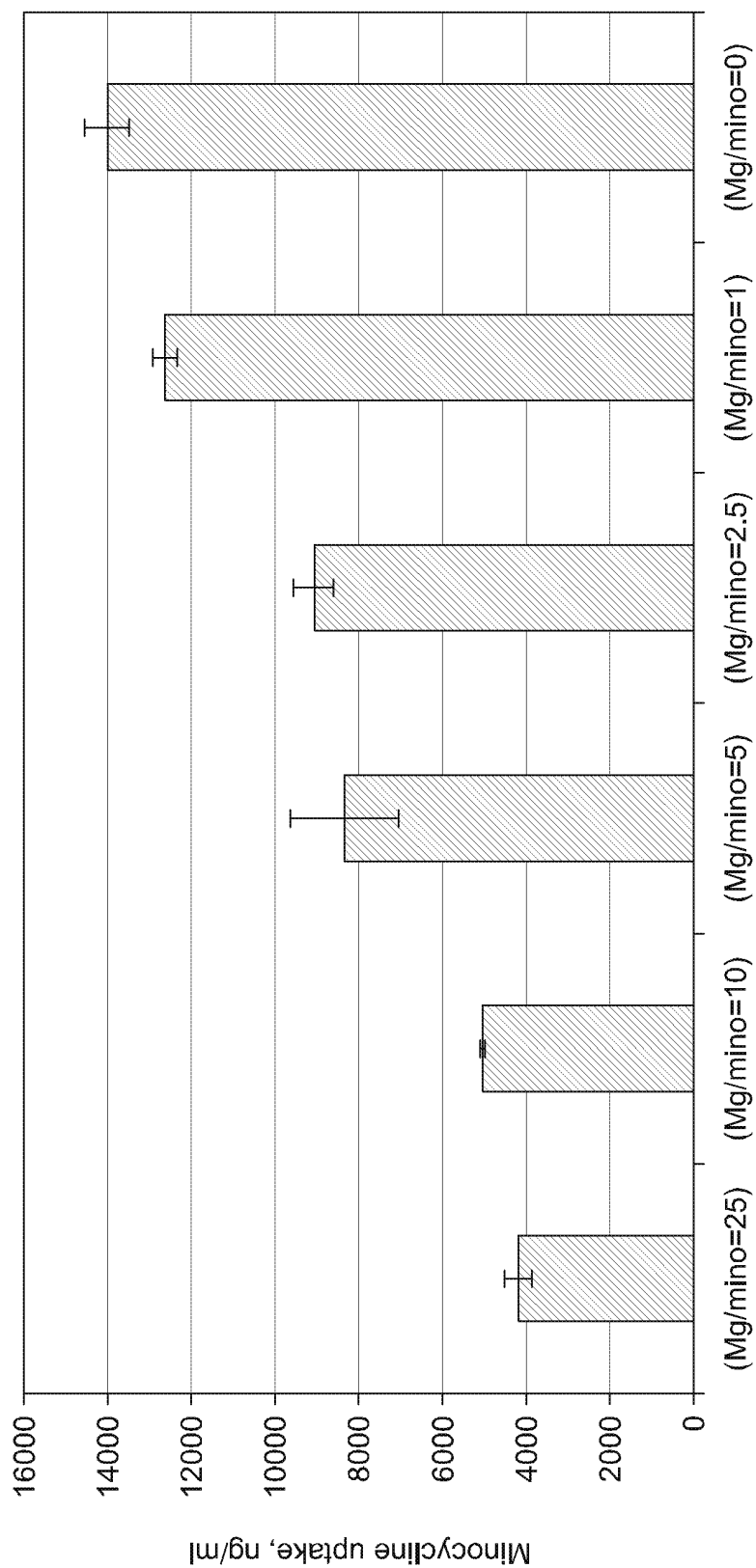


FIG. 6

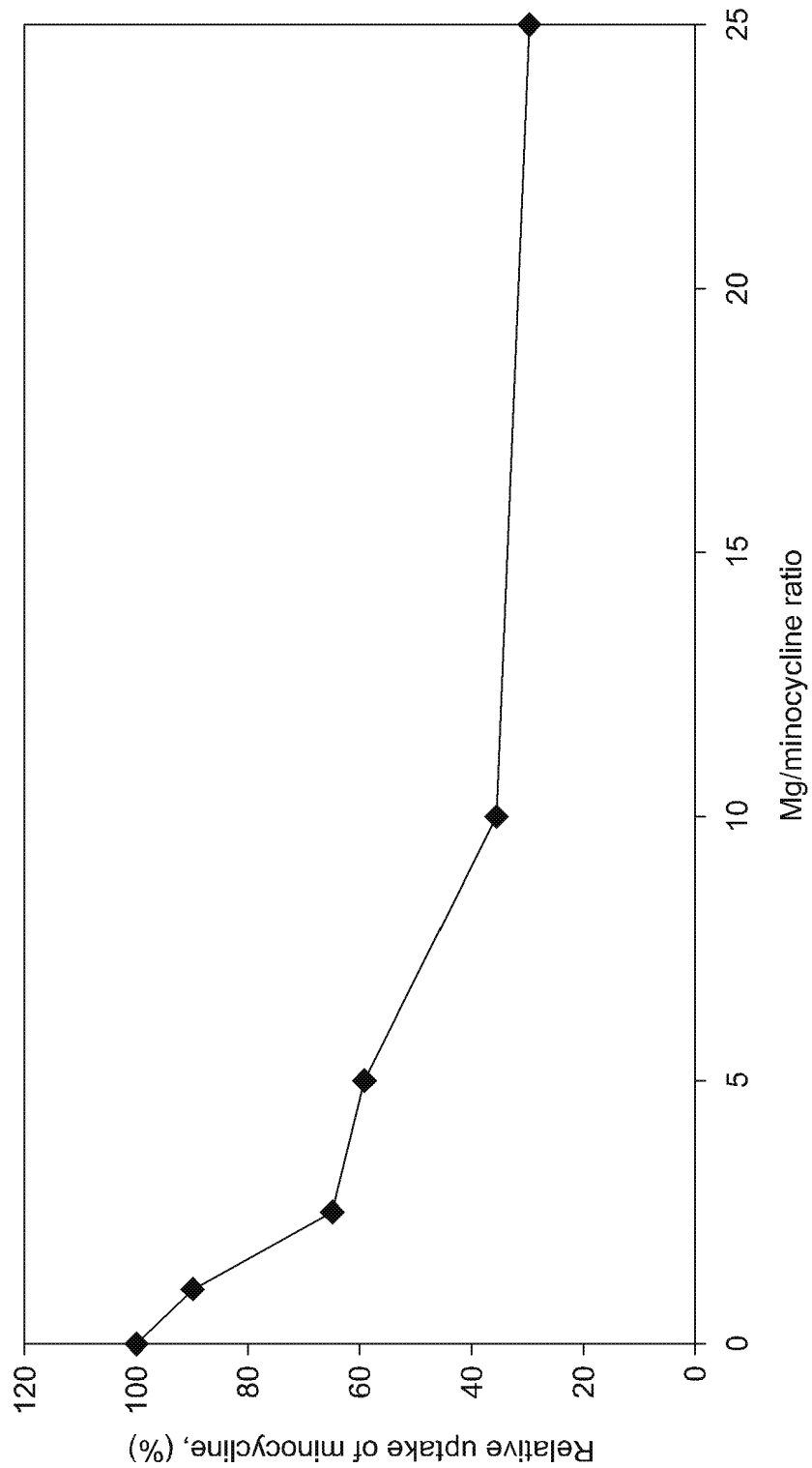


FIG. 7

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TETRACYCLINE COMPOSITIONS**RELATED APPLICATIONS**

This application is a continuation of International Appli-
cation No. PCT/US2011/036351 filed on May 12, 2011,
which claims priority to U.S. Provisional Application No.
61/392,304 filed Oct. 12, 2010, and to U.S. Provisional Appli-
cation No. 61/334,106 filed May 12, 2010, the contents of
which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to tetracycline compositions
and methods for preparing and using the same. Some embod-
iments include a tetracycline with an excess of a divalent or
trivalent cation.

BACKGROUND OF THE INVENTION

Tetracyclines are used as broad spectrum antibiotics to
treat various bacterial infections, such as infections of the
respiratory tract, sinuses, middle ear, urinary tract, and intes-
tines, and can be used in the treatment of gonorrhoea, espe-
cially in patients allergic to β -lactams and macrolides. Tetra-
cyclines interfere with the protein synthesis of Gram positive
and Gram-negative bacteria by preventing the binding of
aminoacyl-tRNA to the ribosome. The action of tetracyclines
is bacteriostatic (preventing growth of bacteria) rather than
killing (bactericidal).

Tetracyclines degrade rapidly to form epitetracycline,
anhydrotetracycline, epianhydrotetracycline, and other deg-
radation products. Once degraded, tetracyclines have small
therapeutic value, since the degradation products have no
therapeutically useful activity. Degradation begins as soon as
the antibiotic is in solution, and continues until reaching an
equilibrium of antibiotic and epimer concentrations. The
equilibrium point is temperature and pH dependent, with
more epimer being formed at higher temperatures and lower
pH. Oxidation and other side reactions cause further deg-
radation. Thus, tetracyclines can have a limited existence in
aqueous environments in their active form. Moreover, the
degradation products of tetracyclines are toxic and can cause
Fanconi syndrome, a potentially fatal disease affecting proxi-
mal tubular function in the nephrons of the kidneys.

There is a need to provide hospital staff with the flexibility
and advantages that come with longer admixture and recon-
stitution times without the need for refrigeration so that for
instance, a hospital pharmacist could prepare a solution the
day before it is needed. Furthermore, often after a natural
disaster such as hurricanes, earthquakes, or tsunamis, access
to refrigeration equipment can be scarce and may be further
impeded by the lack of electricity. Stable formulations of
tetracyclines could be stored as a solution, negating the need
for reconstitution, and allowing its use in inhalers or nebuliz-
ers for outpatient use.

In addition, some tetracyclines can cause tetracycline-in-
duced hemolysis. This hemolysis can lead to venous phlebitis
at the site of injection when administered intravenously,
resulting in irritation and potentially limiting the volumes of
infusion that can be tolerated. Thus, there is a need for for-
mulations of such tetracyclines that reduce the incidence of
hemolysis.

SUMMARY OF THE INVENTION

The present invention relates to tetracycline compositions
and methods for preparing and using the same. Some embod-
iments include a tetracycline with an excess of a divalent or
trivalent cation.

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Some embodiments include pharmaceutical compositions.
In some embodiments the pharmaceutical compositions com-
prise an aqueous solution of minocycline and a divalent or
trivalent cation, wherein the molar ratio of divalent or triva-
lent cation to minocycline is greater than 2:1 and wherein the
solution does not comprise a pharmaceutically acceptable oil
and is suitable for intravenous administration.

In some embodiments the pharmaceutical compositions
comprise an aqueous solution of minocycline and a divalent or
trivalent cation, wherein the molar ratio of divalent or tri-
valent cation to minocycline is greater than 2:1 and wherein
the solution has a pH greater than 4 and less than 5 and is
suitable for intravenous administration.

In some embodiments the pharmaceutical compositions
comprise an aqueous solution of a 7-dimethylamino-tetracy-
cline antibiotic and a divalent or trivalent cation, wherein the
molar ratio of divalent or trivalent cation to 7-dimethylamino-
tetracycline antibiotic is greater than 3:1 and wherein the
solution does not comprise a pharmaceutically acceptable oil,
gluconate, or a pyridine-containing compound, has a pH
greater than 2 and less than 7, and is suitable for intravenous
administration.

In some embodiments, the solution does not comprise
polyoxyethylene hydrogenated castor oil.

In some embodiments, the solution does not comprise an
antioxidant.

In some embodiments, the solution does not comprise a
pyridine-containing compound.

In some embodiments, the solution does not comprise
nicotinamide.

In some embodiments, the solution does not comprise an
alcohol.

In some embodiments, the solution does not comprise
glycerol.

In some embodiments, the solution does not comprise
polyethylene glycol.

In some embodiments, the solution does not comprise glu-
conate.

In some embodiments, the solution does not comprise a
pyrrolidone compound.

In some embodiments, the solution does not comprise a
water-miscible local anaesthetic.

In some embodiments, the water-miscible local anaesthetic
is procaine.

In some embodiments, the solution does not comprise urea.

In some embodiments, the solution does not comprise lac-
tose.

In some embodiments, the solution does not comprise a
dehydrating agent. In some embodiments, the dehydrating
agent is selected from the group consisting of ethyl acetate,
acetic anhydride, absolute ethanol, ethyl acetate, acetic anhy-
dride, and mixtures thereof.

In some embodiments, the solution has a pH of less than 7.

In some embodiments, the solution has a pH of less than 6.
In some embodiments, the solution has a pH of less than 5.

In some embodiments, the solution has a pH greater than 2
and less than 7. In some embodiments, the solution has a pH
greater than 4 and less than 7. In some embodiments, the
solution has a pH greater than 4 and less than 6. In some
embodiments, the solution has a pH greater than 4 and less
than 5.

In some embodiments, the molar ratio of divalent or triva-
lent cation to minocycline is greater than 3:1. In some
embodiments, the molar ratio of divalent or trivalent cation to
minocycline is greater than 5:1. In some embodiments, the
molar ratio of divalent or trivalent cation to minocycline is

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greater than 8:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 10:1.

In some embodiments, the osmolality of the solution is less than 500 mOsm/kg. In some embodiments, the osmolality of the solution is less than 400 mOsm/kg.

In some embodiments, the osmolality of the solution is less than 350 mOsm/kg. In some embodiments, the concentration of minocycline is at least 1 mg/ml. In some embodiments, the concentration of minocycline is at least 5 mg/ml. In some embodiments, the concentration of minocycline is at least 10 mg/ml.

In some embodiments, the solution comprises magnesium sulfate. In some embodiments, the solution comprises magnesium oxide. In some embodiments, the solution comprises magnesium acetate. In some embodiments, the solution comprises magnesium chloride.

In some embodiments, the solution comprises a buffer. In some embodiments, the solution comprises acetate.

In some embodiments, the solution comprises a base. In some embodiments, the base comprises NaOH.

In some embodiments, the cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In some embodiments, the cation is selected from magnesium, calcium, and zinc. In some embodiments, the cation is magnesium.

In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline. In some embodiments, the glycylcycline is tigecycline. In some embodiments, the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the 7-dimethylamino-tetracycline is PTK796.

Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline, MgCl_2 , and NaOH, wherein the Mg to minocycline molar ratio is 5:1, and the pH is greater than 4.5 and less than 5.5.

Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline, MgSO_4 , and sodium acetate, wherein the Mg to minocycline molar ratio is 5:1, the pH is greater than 4.5 and less than 5.5, and the osmolality is greater than 275 mOsm/kg and less than 375 mOsm/kg.

Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline and $\text{Mg}(\text{C}_2\text{H}_3\text{O}_2)_2$, wherein the Mg to minocycline molar ratio is 5:1, and the pH is greater than 4.5 and less than 5.5.

Some embodiments include pharmaceutical compositions comprising 10 mg/ml minocycline, MgSO_4 , and NaOH, wherein the Mg to minocycline molar ratio is 5:1, the pH is greater than 4.5 and less than 5.5, and the osmolality is greater than 150 mOsm/kg and less than 250 mOsm/kg.

Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 5.5 and less than 6.5.

Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 5.5 and less than 6.5.

Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, MgCl_2 , and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 5.5 and less than 6.5.

Some embodiments include pharmaceutical compositions comprising 5 mg/ml tigecycline, MgCl_2 , and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 5.5 and less than 6.5.

Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tige-

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cycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 6.0 and less than 7.0.

Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tigecycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 6.0 and less than 7.0.

Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tigecycline, CaCl_2 , and NaOH, wherein the Ca to tigecycline molar ratio is 5:1, and the pH is greater than 6.0 and less than 7.0.

Some embodiments include pharmaceutical compositions suitable for topical administration comprising 5 mg/ml tigecycline, CaCl_2 , and NaOH, wherein the Ca to tigecycline molar ratio is 12:1, and the pH is greater than 6.0 and less than 7.0.

Some embodiments include water-soluble solid compositions comprising minocycline or a salt thereof and a salt that comprises a divalent or trivalent cation.

Some embodiments include water-soluble solid compositions comprising a 7-dimethylamino-tetracycline antibiotic or a salt thereof and a salt comprising a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and wherein the composition does not comprise gluconate or a pyridine-containing compound.

In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 1:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 2:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 3:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 5:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is at greater than 8:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 10:1.

Some embodiments include compositions in the form of a lyophile.

In some embodiments, the salt is magnesium sulfate.

In some embodiments, the salt is calcium chloride.

In some embodiments, the composition comprises sodium acetate.

In some embodiments, the composition comprises NaOH.

In some embodiments, the salt is selected from magnesium chloride, magnesium bromide, magnesium sulfate, calcium chloride, calcium bromide, calcium sulfate, zinc chloride, gallium chloride, magnesium malate, magnesium citrate, magnesium acetate, calcium citrate, zinc acetate, and zinc citrate.

In some embodiments, the composition does not comprise an antioxidant.

In some embodiments, the composition does not comprise a pyridine-containing compound. In some embodiments, the composition does not comprise nicotinamide.

In some embodiments, the composition does not comprise gluconate.

In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline. In some embodiments, the glycylcycline is tigecycline. In some embodiments, the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the 7-dimethylamino-tetracycline is PTK796.

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Some embodiments include methods for preparing a pharmaceutical composition comprising dissolving the water-soluble solid composition of any one of the water-soluble solid compositions provided herein in water to form a solution

Some embodiments include methods for preparing a pharmaceutical composition comprising dissolving a 7-dimethylamino-tetracycline in a solution comprising a divalent or trivalent cation.

Some embodiments include methods for preparing a pharmaceutical composition comprising dissolving a 7-dimethylamino-tetracycline in a solution comprising a divalent or trivalent cation; adjusting the pH of the solution; and lyophilizing the composition.

In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline. In some embodiments, the glycylcycline is tigecycline.

In some embodiments, the pH of the solution is adjusted to be less than 6. In some embodiments, the pH of the solution is adjusted to be less than 5.

In some embodiments, the pH of the solution is adjusted to be greater than 2 and less than 7. In some embodiments, the pH of the solution is adjusted to be greater than 4 and less than 7. In some embodiments, the pH of the solution is adjusted to be greater than 4 and less than 6. In some embodiments, the pH of the solution is adjusted to be greater than 4 and less than 5.

In some embodiments, adjusting the pH comprises adding an acid. In some embodiments, the acid is HCl.

In some embodiments, adjusting the pH comprises adding a base. In some embodiments, the base is NaOH.

In some embodiments, adjusting the pH comprises forming a buffer. In some embodiments, forming the buffer comprises adding sodium acetate.

In some embodiments, the divalent or trivalent cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In some embodiments, the cation is selected from magnesium, calcium, and zinc. In some embodiments, the cation is magnesium.

Some embodiments include kits comprising a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises minocycline in an amount such that the molar ratio of the divalent or trivalent cation to minocycline is greater than 2:1.

Some embodiments include kits comprising a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises a 7-dimethylamino-tetracycline antibiotic in an amount such that the molar ratio of the divalent or trivalent cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1.

In some embodiments, the diluent comprises an acid. In some embodiments, the acid is HCl.

In some embodiments, the diluent comprises a base. In some embodiments, the base is NaOH.

In some embodiments, the diluent comprises a buffer. In some embodiments, the diluent comprises sodium acetate.

In some embodiments, the pH of the diluent is greater than pH 6 and less than pH 8.

In some embodiments, the divalent or trivalent cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In some

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embodiments, the cation is selected from magnesium, calcium, and zinc. In some embodiments, the cation is magnesium.

In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 3:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 5:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is at greater than 8:1. In some embodiments, the molar ratio of divalent or trivalent cation to the minocycline or the 7-dimethylamino-tetracycline antibiotic is greater than 10:1.

In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline. In some embodiments, the glycylcycline is tigecycline. In some embodiments, the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the 7-dimethylamino-tetracycline is PTK796.

Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition of any one of the pharmaceutical compositions provided herein to the subject via an intravenous route.

Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition made according to any one of the methods of preparing a pharmaceutical compositions provided herein to the subject via an intravenous route.

In some embodiments, the intravenous administration includes administering less than 200 ml of the composition.

In some embodiments, the intravenous administration includes administering the composition in less than 60 minutes.

Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition of any one of the pharmaceutical compositions provided herein to the subject via a topical route.

Some embodiments include methods of treating or preventing a bacterial infection in a subject, comprising administering the pharmaceutical composition made according to any one of the methods of preparing a pharmaceutical compositions provided herein to the subject via a topical route.

Some embodiments include compositions comprising tigecycline and a divalent or trivalent cation, wherein the molar ratio of said divalent or trivalent cation to said tigecycline is greater than 1:1.

In some embodiments, the tigecycline and divalent or trivalent cation are in aqueous solution.

In some embodiments, the molar ratio of said divalent or trivalent cation to said tigecycline is greater than 3:1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a graph of percent hemolysis of rabbit red blood cells incubated with various concentrations of minocycline in various solutions relative to hemolysis in water, in which the minocycline solutions formulated with divalent cations were adjusted to pH 5.85.

FIG. 2 shows a graph of percent hemolysis of rabbit red blood cells incubated with various concentrations of minocycline in various solutions relative to hemolysis in water.

FIG. 3 depicts a graph of rabbit RBC hemolysis caused by minocycline formulated in different ratios of MgSO_4 .

FIG. 4 depicts a graph of rabbit RBC hemolysis caused by minocycline formulated in different ratios of MgCl_2 .

FIG. 5 depicts a graph of rabbit RBC hemolysis caused by minocycline formulated in different ratios of CaCl_2 .

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FIG. 6 depicts a graph for minocycline uptake by HVEC at various concentrations of divalent cation.

FIG. 7 depicts a graph for minocycline uptake by HVEC at various concentrations of divalent cation.

DETAILED DESCRIPTION

The present invention relates to tetracycline compositions and methods for preparing and using the same. Some embodiments include a tetracycline with an excess of a metal cation. In some embodiments, the compositions have improved stability against both oxidative degradation and epimerization. Some such compositions are therefore more stable when dissolved, lyophilized, reconstituted, and/or diluted than other compositions. Some embodiments also provide compositions having a lower level of tetracycline-induced hemolysis and resulting phlebitis.

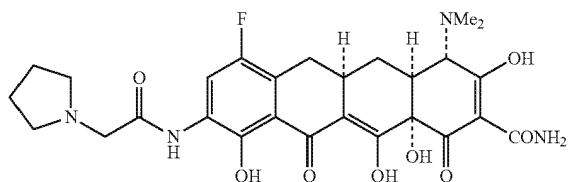
It was unexpectedly discovered that the incidence of tetracycline-induced hemolysis can be greatly decreased by formulating the tetracycline with divalent or trivalent cations. In some embodiments, high molar ratios of divalent or trivalent cations to tetracycline antibiotics significantly decreases hemolysis.

It was also unexpectedly discovered that the stability of aqueous solutions of tetracyclines can be greatly increased by the addition of divalent or trivalent cations. In some embodiments, the stability of aqueous solutions of tetracyclines increase with higher molar ratios of divalent or trivalent cations to tetracycline. Indeed, some such solutions were found to be stable for several weeks at 37° C.

In certain compositions, the solubility of a tetracycline antibiotic is decreased in an aqueous solution comprising a multivalent cation. It has been unexpectedly discovered that increasing the molar ratio of multivalent cation to such tetracycline antibiotics can increase the solubility of the tetracycline. Accordingly, some embodiments described herein provide solutions of a tetracycline with improved solubility.

Compositions

Some embodiments include compositions comprising a tetracycline antibiotic or a salt thereof in combination with a divalent or trivalent cation. Tetracyclines include a family of structurally-related compounds that may have broad-spectrum antibiotic activities. Examples of tetracyclines include Tetracycline, Chlortetracycline, Oxytetracycline, Demeclocycline, Doxycycline, Lymecycline, Meclocycline, Methacycline, Minocycline, Rolitetracycline, Minocycline, Tigecycline, Chlorocycline, Glycylcyclines, Aminomethylcyclines, TP434, and PTK796, (also known as BAY 73-7388 and MK2764). The structure of TP434 is provided below:

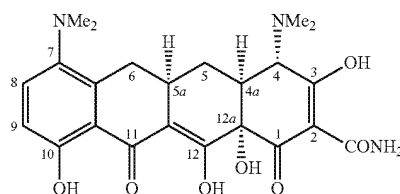


In one embodiment, the tetracycline antibiotic is selected from the group consisting of tetracycline, oxytetracycline, doxycycline, chlorocycline, minocycline, glycylcyclines and aminomethylcyclines. In one embodiment, the tetracycline is a glycylcycline. In one embodiment, the glycylcycline is tigecycline. In one embodiment, the tetracycline is an aminomethylcycline. In one embodiment, the aminomethylcycline is

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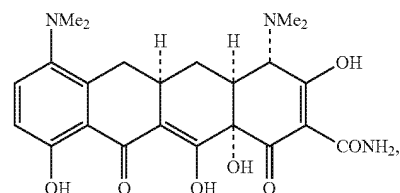
PTK796, also known as BAY 73-7388 and MK2764. In another embodiment, the tetracycline is selected from the group consisting of tetracycline, minocycline, tigecycline and PTK796. In one embodiment, the tetracycline antibiotic is tetracycline. In one embodiment, of the invention, the tetracycline is minocycline. In one embodiment, of the invention, the tetracycline is tigecycline. In yet another embodiment, of the invention, the tetracycline is PTK796. Some embodiments include a salt of a tetracycline antibiotic.

In some embodiments, the tetracycline antibiotic is a 7-dimethylamino-tetracycline. 7-dimethylamino-tetracyclines contain an additional dimethylamino substituent at the 7-position on the four-ring core. The 7-position is indicated on following numbered structure of minocycline:

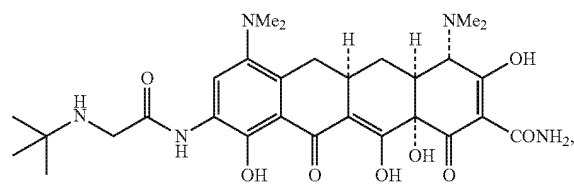


Examples of 7-dimethylamino-tetracyclines include minocycline, a glycylcycline (e.g., tigecycline) and PTK796. Example structures of such compounds include:

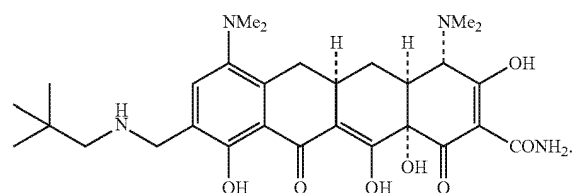
Minocycline:



Tigecycline:



and
PTK796:

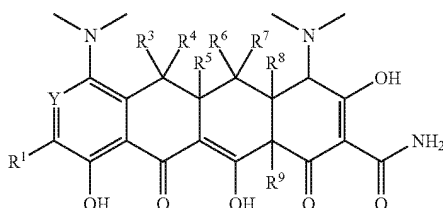


As used herein, "glycylcyclines" are 7-dimethylamino-tetracyclines having an N-alkylglycylamido side chain at position 9 of the four-ring core.

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In some embodiments, the 7-dimethylamino-tetracycline antibiotic has the structure:



or tautomers thereof, wherein:

R¹ is selected from H, $-(CH_2)_nNHC(O)(CH_2)_nR^{10}$, and $-(CH_2)_nR^{10}$, where each n is independently an integer from 0 to 3, and

R¹⁰ is selected from $-NH-C_{1-8}alkyl$, $-NH-C_{1-8}cycloalkyl$, and a saturated 4-to-7-membered heterocycle containing one nitrogen atom, wherein if the connecting atom of R¹⁰ is carbon, the nitrogen atom is optionally substituted by C₁-C₄alkyl;

Y is CR² or N; and

R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from H, $-OH$, halogen, and C₁₋₄alkyl; or

optionally R¹ and R² together form a 6-membered aryl or heteroaryl ring, optionally substituted by one or two groups independently selected from H, R¹, $-OH$, halogen, and C₁₋₄alkyl.

In some embodiments, each of R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are hydrogen.

As used herein, "alkyl" refers to a straight- or branched-chain moiety containing only carbon and hydrogen. Alkyls may have any degree of saturation. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tertbutyl.

As used herein, "cycloalkyl" refers to a ring or ring system comprising only carbon in the ring backbone. Cycloalkyls may include one or more fused or bridged rings. Cycloalkyls may have any degree of saturation provided that at least one ring is not aromatic. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexenyl.

As used herein, "heterocycle" refers to a ring or ring system comprising at least one heteroatom in the ring backbone. Heterocycles may include one or more fused or bridged rings. Heterocycles may have any degree of saturation provided that at least one ring is not aromatic. Examples include pyrrolidine, piperidine, piperazine, and morpholino.

As used herein, "aryl" refers to an aromatic ring or ring system comprising only carbon in the ring backbone. Aryls may include one or more fused rings. Examples include phenyl and naphthyl.

As used herein, "heteroaryl" refers to an aromatic ring or ring system comprising at least one heteroatom in the ring backbone. Heteroaryls may include one or more fused rings. Examples include imidazole, oxazole, pyridine, and quinoline.

Some compositions include at least one multivalent cation. Multivalent cations include bivalent and trivalent cations, e.g., metal cations. The metal cations include common multivalent metal cations. In some embodiments, the metal cations include iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium.

Some compositions include a salt that comprises the cation. In one embodiment, the salts are inorganic metal salts and can include anhydrous, hydrated and solvated forms of the salts. In another embodiment, the salts are organic metal salts

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and include but are not limited to the anhydrous, hydrated and solvated forms of the salt. In one embodiment, the anion in the inorganic metal salts can include chloride, bromide, oxide, and sulfate salts. In one embodiment, the organic metal salts are those where the anion of the salt is selected from the GRAS (generally regarded as safe) list such as but not limited to acetate, citrate, gluconate, and malate salts. Suitable anions may also be found in see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. In some embodiments, a composition can include more than one type of metal cation. In some such embodiments, the anions for each metal salt can be the same. In another embodiment, the anions for each metal salt are different. In another embodiment, the metal cation is included in the compositions provided herein as different salts of the same cation. In one embodiment the metal salts are all inorganic. In another embodiment, the metal salts are all organic. In yet another embodiment, the metal salts are a combination of organic and inorganic salts.

Examples of inorganic metal salts that may be included in the compositions provided herein include magnesium chloride (including the hexahydrate), magnesium bromide, magnesium sulfate (including the heptahydrate), magnesium oxide, calcium chloride, calcium bromide, calcium sulfate, zinc chloride, and gallium chloride. Examples of inorganic metal salts that may be included in the compositions provided herein include magnesium malate, magnesium gluconate, magnesium citrate, magnesium acetate (including the trihydrate), calcium gluconate, calcium citrate, zinc gluconate, zinc acetate, and zinc citrate. The salts described herein include both their anhydrous and hydrated forms.

Some compositions provided herein include a tetracycline and divalent or trivalent cation, e.g., metal cation at particular molar ratios of divalent or trivalent cation to tetracycline. For example, some embodiments include compositions comprising a tetracycline and a divalent or trivalent cation, wherein the molar ratio of said divalent or trivalent cation to said tetracycline is greater than about 1:1. In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is greater than about 2:1, greater than about 3:1, greater than about 4:1, greater than about 5:1, greater than about 6:1, greater than about 7:1, greater than about 8:1, greater than about 9:1, greater than about 10:1, greater than about 11:1, greater than about 12:1, greater than about 13:1, greater than about 14:1, greater than about 15:1, greater than about 16:1, greater than about 17:1, greater than about 18:1, greater than about 19:1, greater than about 20:1, greater than about 21:1, greater than about 22:1, greater than about 23:1, greater than about 24:1, greater than about 25:1, greater than about 26:1, greater than about 27:1, greater than about 28:1, greater than about 29:1, and greater than about 30:1. In some embodiments, the molar ratio is greater than about 35:1, greater than about 40:1, greater than about 45:1, and greater than about 50:1.

In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is between about 1:1 to about 30:1, between about 5:1 to about 30:1, between about 10:1 to about 30:1, and between about 20:1 to about 30:1. In some such embodiments, the molar ratio of the divalent or trivalent cation to the tetracycline is between about 1:1 to about 50:1, between about 5:1 to about 50:1, between about 10:1 to about 50:1, and between about 20:1 to about 50:1.

In some embodiments, the relative amounts of metal cation present in the compositions of the invention are those amounts which are in excess of the 1:1 metal cation: a tetracycline stoichiometry for each metal cation. In one embodiment of the invention, the metal cation to a tetracycline molar

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ratio ranges from 5:1 to 100:1. In another embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 5:1 to 50:1. In yet another embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 5:1 to 30:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 5:1 to 10:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 10:1 to 20:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio ranges from 10:1 to 15:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 5:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 10:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 12:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 15:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 20:1. In one embodiment of the invention, the metal cation to a tetracycline molar ratio is 30:1.

Some compositions include carbohydrates in addition to a divalent or trivalent cation. Suitable carbohydrates are those carbohydrates capable of reducing degradation of the tetracycline in at least one solid form prepared in at least one pH environment when compared to a solid form of a tetracycline prepared at the same pH environment lacking suitable carbohydrates. In one embodiment, the pH environment ranges from 3.0 to about 7.0, such as pHs ranging from about 4.0 to about 6.5, from about 5.0 to about 6.5, and from about 5.5 to about 6.5. In one embodiment, at least one solid form is chosen from powders and lyophilized cakes of a tetracycline. In another embodiment of the invention, carbohydrates are those carbohydrates capable of reducing degradation of the tetracycline in solution prepared in at least one pH environment when compared to a solution of a tetracycline prepared at the same pH environment lacking suitable carbohydrates. In one embodiment, the pH environment ranges from 3.0 to about 7.0, such as pHs ranging from about 4.0 to about 6.5, from about 5.0 to about 6.5, and from about 5.5 to about 6.5.

Suitable carbohydrates include mono and disaccharides e.g. an aldose monosaccharide or a disaccharide. Examples of suitable carbohydrates include but are not limited to the anhydrous, hydrated and solvated forms of compounds such as trehalose, lactose, mannose, sucrose and glucose. In one embodiment of the invention, the carbohydrate is a disaccharide. In another embodiment of the invention, the disaccharide is trehalose, lactose or sucrose. In yet another embodiment of the invention, the carbohydrate is lactose, including its different forms such as anhydrous lactose, lactose monohydrate or any other hydrated or solvated form of lactose. In one embodiment of the invention, the carbohydrate is trehalose, including its different forms such as anhydrous trehalose, trehalose dihydrate or any other hydrated or solvated form of trehalose.

In one embodiment of the invention, the suitable carbohydrate used is lactose monohydrate and the molar ratio of tigecycline to lactose monohydrate in the lyophilized powder or cake is between 1:0.2 to about 1:5. In another embodiment of the invention, the tigecycline to lactose monohydrate molar ratio is between 1:1.6 to about 1:3.3.

Some compositions include an antioxidant. Antioxidants can be used to prevent or reduce the oxidation of tetracyclines either in solution or in the solid state. Examples of antioxidants include ascorbic acid, citric acid, trehalose, butylated hydroxyl toluene (BHT), butylated hydroxyl anisole (BHA), sodium metabisulfite, d,l- α -tocopherol, and gentisic acid.

It will be appreciated that the compositions provided herein can include aerosols, liquids, and solids. Solids can

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include, for example, lyophilized compositions, such as powders, cakes, or the like. Such solids may be water soluble so that they may be used to prepare aqueous solutions. Liquids can include solutions or suspensions, which may be prepared from solid compositions. Liquids include solutions that may be prepared prior to manufacturing procedures such as lyophilization. In one embodiment, the solution may be stored for several hours prior to lyophilization in order to provide greater manufacturing flexibility. Liquids also include solutions that are prepared by reconstitution for use in administration to a patient. Some compositions include solutions made from the lyophilized powder or cake by, for example, reconstitution with saline or other pharmaceutically acceptable diluents. Pharmaceutically acceptable diluents are those listed by USP such as but not limited to water for injection, saline solution, lactated Ringer's solution for injection or dextrose solution. Some compositions include solutions resulting from diluting those reconstituted solutions with pharmaceutically acceptable diluents for use in intravenous bags.

In some embodiments, the pH of a liquid composition provided herein, such as an aqueous solution, is between about pH 2.0 to about pH 8.0, between about pH 2.5 to about pH 7.5. In some embodiments, the pH of the composition is between about pH 3.0 to about pH 7.0, between about pH 3.5 to about pH 6.5, between about pH 4.0 to about pH 6.5, between about pH 4.0 to about pH 6.0, between about pH 4.5 to about pH 6.0, between about pH 4.5 to about pH 5.5, between about pH 5.0 to about pH 5.5, between about pH 5.5 to about pH 6.5, between about pH 3.5 to about pH 4.5. In some embodiments, the pH of the solution is less than pH 7, less than pH 6, less than pH 5, less than pH 4, less than pH 3, and less than pH 2. In some embodiments the pH of the solution is greater than pH 2 and less than pH 7, greater than pH 4 and less than pH 7, greater than pH 4 and less than pH 6, and greater than pH 4 and less than pH 5.

In some embodiments, liquid compositions, such as an aqueous solution, can have an osmolality from about 300 mOsmol/kg to about 500 mOsmol/kg, from about 325 mOsmol/kg to about 450 mOsmol/kg, from about 350 mOsmol/kg to about 425 mOsmol/kg, or from about 350 mOsmol/kg to about 400 mOsmol/kg. In some embodiments, the osmolality of the formulation is greater than about 300 mOsmol/kg, about 325 mOsmol/kg, about 350 mOsmol/kg, about 375 mOsmol/kg, about 400 mOsmol/kg, about 425 mOsmol/kg, about 450 mOsmol/kg, about 475 mOsmol/kg, or about 500 mOsmol/kg. In some embodiments, liquid compositions can have an osmolality from about 200 mOsmol/kg to about 1250 mOsmol/kg. In another embodiment, the osmolality is between about 250 mOsmol/kg and about 1050 mOsmol/kg. In another embodiment, the osmolality is between about 250 mOsmol/kg and about 750 mOsmol/kg. In another embodiment, the osmolality is between about 350 mOsmol/kg and about 500 mOsmol/kg. In some embodiments, the osmolality of the solution is less than 500 mOsmol/kg, 450 mOsmol/kg, 400 mOsmol/kg, 350 mOsmol/kg, or 300 mOsmol/kg.

Some embodiments include an aqueous solution comprising a tetracycline having a concentration of at least 1 mg/ml, 5 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 35 mg/ml, 40 mg/ml, 45 mg/ml, or 50 mg/ml.

Some embodiments include an aqueous solution comprising a buffer, such as an acetate buffer (e.g., provided as sodium acetate), wherein the acetate has a concentration of at least 0.01 M, 0.02 M, 0.03 M, 0.04 M, 0.05 M, 0.1 M, 0.15 M, 0.20 M, 0.25 M, 0.30 M, 0.35 M, 0.40 M, 0.45 M, 0.50 M, 0.55 M, 0.60 M, 0.65 M, 0.70 M, 0.75 M, 0.80 M, 0.85 M, 0.90 M, or 0.95 M.

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Some embodiments include an aqueous solution comprising a salt comprising divalent or trivalent cation, such as a magnesium salt (e.g., magnesium chloride or magnesium sulfate), having a concentration of at least 0.01 M, 0.02 M, 0.03 M, 0.04 M, 0.05 M, 0.1 M, 0.15 M, 0.20 M, 0.25 M, 0.30 M, 0.35 M, 0.40 M, 0.45 M, 0.50 M, 0.55 M, 0.60 M, 0.65 M, 0.70 M, 0.75 M, 0.80 M, 0.85 M, 0.90 M, or 0.95 M.

In one embodiment, liquid compositions, such as aqueous solutions, have a permeant ion concentration from about 30 mM to about 300 mM. In another embodiment, the permeant ion concentration is between 50 mM and 200 mM. In another embodiment, the permeant ion is selected from the list consisting of chloride and bromide. In another embodiment the permeant ion is chloride. In another embodiment, the permeant ion is bromide.

In some embodiments, aqueous solution compositions comprise a buffer. For example, in some embodiments, the solution comprises acetate. In some embodiments, aqueous solution compositions comprise a base such as NaOH. In some embodiments, aqueous solution compositions comprise an acid such as HCl.

It is contemplated that in some embodiments, reconstituted solutions may be stored in a reconstituted state at room temperature prior to further dilution for injection or topical administration. In some embodiments, storage times at room temperature after reconstitution are much longer than current compositions. In some embodiments, admixing can occur, for example, in an intravenous bag. To prepare an admixture, sufficient reconstituted solution is mixed in an intravenous bag containing a pharmaceutically acceptable diluent such as saline or dextrose solution such as 5DW.

The concentration of admixtures may easily be determined by those of ordinary skill in the art. The time available for admixture of reconstituted solutions from the compositions may be much longer than those of previously described formulations. Storage times of the admixtures at room temperature may also be much longer than those of the existing compositions. Once admixed, the tetracycline solution is ready for administration by or to the patient. The admixture may be administered alone or together with another pharmaceutical agent or composition.

In some embodiments, the composition does not comprise a pharmaceutically acceptable oil. In some embodiments, an oil can refer to a hydrocarbon compound that is liquid at room temperature and insoluble in water. Examples of pharmaceutically acceptable oils include polyoxyethylene hydrogenated castor oils such as PEG-40 hydrogenated castor oil and PEG-50 hydrogenated castor oil. More examples of pharmaceutically acceptable oils include olive oil, sesame oil, soybean oil, safflower oil, cottonseed oil, corn oil, sunflower oil, arachis oil, coconut oil, an omega-3 polyunsaturated oil, and an omega-3 marine triglyceride.

In some embodiments, the composition does not comprise a pyridine-containing compound. In one embodiment, the pyridine-containing compound is nicotinamide.

Although some embodiments include gluconate (e.g., as the gluconate salt of a divalent or trivalent metal cation), other embodiments include compositions that do not comprise gluconate.

In some embodiments, the composition does not comprise a non-aqueous tetracycline-solubilizing co-solvent. Such solubilizing co-solvents can include the oil, pyridine-containing compound, and gluconate described above.

Although some embodiments include an antioxidant, other embodiments include compositions that do not comprise an antioxidant (e.g., sodium or magnesium formaldehyde sul-

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foxylate; sodium sulfite, metabisulfite or bisulfite; sodium sulfide; alpha-monothioglycerol (also referred to as thioglycerol); and thiosorbitol).

Other various embodiments include compositions that do not include one or more of an alcohol (e.g., a polyhydric alcohol, such as, propylene glycol, ethylene glycol), glycerol, polyethylene glycol, a pyrrolidone-containing compound, a water-miscible local anaesthetic (e.g., procaine, tetracaine), urea, lactose, or a dehydrating agent (e.g., ethyl acetate, acetic anhydride, absolute ethanol, ethyl acetate, acetic anhydride, and mixtures thereof).

Some embodiments include compositions comprising a 7-dimethylamino-tetracycline and a cation. In some such embodiments the 7-dimethylamino-tetracycline is minocycline. In some embodiments, the minocycline is minocycline HCl. In some embodiments the cation comprises Mg^{2+} . In some embodiments, the compositions include a salt selected from $MgCl_2$ (e.g., $MgCl_2 \cdot 6H_2O$), $MgSO_4$ (e.g., $MgSO_4 \cdot 7H_2O$) and magnesium acetate (e.g., $Mg(CH_3COO)_2 \cdot 3H_2O$). In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than 10:1, 20:1, 30:1, 40:1, or 50:1. Some embodiments include a buffer. In some such embodiments, the buffer includes NaOH, or sodium acetate (e.g., $NaCH_3COO \cdot 3H_2O$).

Some compositions comprise minocycline and $MgCl_2 \cdot 6H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a base comprising NaOH. Some such embodiments are suitable for intravenous use.

Some compositions comprise minocycline and $MgSO_4 \cdot 7H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising $NaCH_3COO \cdot 3H_2O$ with a pH in the range 4.5-5.5 and an osmolality in the range of about 275-375 mOsm/kg. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH and osmolality of a reconstituted solution can have a pH in the range 4.5-5.5 and an osmolality in the range of about 275-375 mOsm/kg. Some such embodiments are suitable for intravenous use.

Some embodiments comprise minocycline and $Mg(CH_3COO)_2 \cdot 3H_2O$ with a Mg to minocycline molar ratio of about 5:1 with no buffer added. Some such embodiments are suitable for intravenous use.

Some embodiments include minocycline and $MgSO_4 \cdot 7H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a base comprising NaOH with a pH in the range 5.5-6.5. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 5.5-6.5. Some such embodiments are suitable for intravenous use.

Some embodiments comprise tigecycline and $MgSO_4 \cdot 7H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising NaOH with a pH in the range 5.5-6.5. Some embodiments comprise tigecycline and $MgSO_4 \cdot 7H_2O$ with a Mg to minocycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 5.5-6.5. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 5.5-6.5. Some such embodiments are suitable for intravenous use.

Some embodiments comprise tigecycline and $MgCl_2 \cdot 6H_2O$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising NaOH with a pH in the range

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5.5-6.5. Some embodiments comprise tigecycline and $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ with a Mg to minocycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 5.5-6.5. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 5.5-6.5. Some such embodiments are suitable for intravenous use.

Some embodiments comprise tigecycline and $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ with a Mg to minocycline molar ratio of about 5:1 in a buffer comprising NaOH with a pH in the range 6.0-7.0. Some embodiments comprise tigecycline and $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ with a Mg to minocycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 6.0-7.0. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 6.0-7.0. Some such embodiments are suitable for topical use. Some such compositions comprise tigecycline with greater than 90%, 95%, or 98% stability for at least 30 days. Some embodiments include compositions comprising an additional constituent such as benzalkonium chloride, a steroid such as hydrocortisone, dexamethasone, thonzonium bromide, tyloxapol, an antiseptic agent such as boric acid, a preservative such as benzalkonium chloride.

Some embodiments comprise tigecycline and $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ with a Ca:minocycline:molar ratio of about 5:1 in a base comprising NaOH with a pH in the range 6.0-7.0. Some embodiments comprise tigecycline and $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ with a Ca to tigecycline molar ratio of about 12:1 in a base comprising NaOH with a pH in the range 6.0-7.0. Some such compositions can be prepared as an aqueous solution and lyophilized. As will be understood by a skilled artisan, the pH of a reconstituted solution can have a pH in the range 6.0-7.0. Some such embodiments are suitable for topical use. Some such compositions comprise tigecycline with greater than 90%, 95%, 98% stability for at least 30 days. Some embodiments include compositions comprising an additional constituent such as benzalkonium chloride, a steroid such as hydrocortisone, dexamethasone, thonzonium bromide, tyloxapol, an antiseptic agent such as boric acid, a preservative such as benzalkonium chloride.

Some embodiments include pharmaceutical compositions comprising an aqueous solution of minocycline and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to minocycline is greater than 2:1. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than about 3:1, greater than about 5:1, greater than about 8:1, greater than about 10:1. In some embodiments, the divalent or trivalent cation is selected from iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium. In particular embodiments, the divalent or trivalent cation is selected from magnesium, calcium, and zinc. In some embodiments, the solution comprises magnesium sulfate and/or magnesium oxide. In particular embodiments, the composition is suitable for intravenous administration.

More embodiments include a pharmaceutical composition comprising an aqueous solution of an 7-dimethylamino-tetracycline antibiotic and a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than 3:1 and wherein the solution does not comprise an oil, gluconate, or a pyridine-containing compound, has a pH greater than 2 and less than 7, and is suitable for intravenous administration. In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and glycylicyclines (e.g. tigecycline).

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Some embodiments include a water-soluble solid composition, comprising minocycline or a salt thereof and a salt that comprises a divalent or trivalent cation. In some embodiments, the molar ratio of divalent or trivalent cation to minocycline is greater than about 1:1, greater than about 2:1, greater than about 3:1, greater than about 5:1, greater than about 8:1, greater than about 10:1. In some embodiments, the salt is selected from magnesium chloride, magnesium bromide, magnesium sulfate, calcium chloride, calcium bromide, calcium sulfate, zinc chloride, gallium chloride, magnesium malate, magnesium gluconate, magnesium citrate, calcium gluconate, calcium citrate, zinc gluconate, zinc acetate, and zinc citrate. In preferred embodiments, the salt is magnesium sulfate. In some embodiments, the composition comprises sodium acetate. In certain embodiments, the composition does not comprise an antioxidant, a pyridine-containing compound (e.g., nicotinamide), or gluconate.

More embodiments include water-soluble solid compositions comprising a 7-dimethylamino-tetracycline antibiotic and a salt comprising a divalent or trivalent cation, wherein the molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than 3:1 and wherein the composition does not comprise gluconate or a pyridine-containing compound. In some embodiments, the 7-dimethylamino-tetracycline is selected from minocycline, glycylicyclines (e.g. tigecycline) and PTK796.

In some embodiments, the water-soluble compositions described above are in the form of a lyophile.

Methods of Preparation

Some embodiments of the present invention include methods for preparing the compositions described herein. Some such methods include combining a tetracycline antibiotic and a divalent or trivalent cation. Some methods further comprise modifying the pH of the compositions. In some methods, modifying the pH comprises adjusting the pH with a pH modifying agent. Examples of pH modifying agents include hydrochloric acid, gentisic acid, lactic acid, citric acid, acetic acid, phosphoric acid, sodium hydroxide, sodium bicarbonate and sodium carbonate. In some embodiments, the pH-modifying agent includes any pharmaceutically acceptable acid, base or buffer capable of adjusting the pH of a tetracycline antibiotic/metal cation solution to between about 3.0 to about 7.0, about 4.0 to about 5.0, about 5.0 to 6.0, about 5.5 to 6.5, about 6.0 to 6.5 or about 4.2 to 4.8. In some embodiments, the acid, base or buffer is used to adjust the pH of a tetracycline antibiotic/metal cation solution to a pH less than 7, 6, 5, or 4. In some embodiments, the acid, base or buffer is used to adjust the pH of a tetracycline antibiotic/metal cation solution to a pH greater than 2 and less than 7, greater than 4 and less than 7, greater than 4 and less than 6, and greater than 4 and less than 5. Examples of such acids include but are not limited to hydrochloric acid, including 1.0 N HCl, gentisic acid, lactic acid, citric acid, acetic acid and phosphoric acid. Examples of suitable buffers include as components succinates and acetate. Examples of such bases include but are not limited to aqueous solutions of sodium hydroxide, including 1.0 N NaOH solution, sodium bicarbonate and sodium carbonate.

Compositions of the invention may be prepared via a number of acceptable methods. For example, the metal salts are dissolved in water and the tetracycline antibiotic is added to this solution. Alternatively, the antibiotic is dissolved first and the metal salt is added to the solution. The pH of the solution is then adjusted with an acid, a base or buffer. Other optional agents such as an antioxidant or carbohydrate are then dissolved in the solution. The final solution may be then be used

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directly in therapy or lyophilized to dryness to form a lyophilized powder or cake for later reconstitution.

In another example, a tetracycline antibiotic may be dry blended with the metal salts and other optional ingredients, and the residual mixture dissolved in water. After the pH of the solution is adjusted, the solution may then be used in therapy or lyophilized to dryness to form a powder or cake.

Lyophilization of solutions described herein may be accomplished by any pharmaceutically acceptable means. Once lyophilized, the compositions of the invention may be stored under an inert gas, such as nitrogen, to further slow the degradation process.

The tetracycline antibiotic used in the various preparation techniques may be any solid-state form of the tetracycline that is sufficiently soluble in water. Such solid-state forms include crystalline tetracycline polymorphs, amorphous forms and salts.

One embodiment for preparing aminocycline-containing pharmaceutical composition includes dissolving minocycline and a salt that comprises a divalent or trivalent cation in water to form a solution and adjusting the pH of the solution to be less than about 7, less than about 6, less than about 5, less than about 4, or less than about 3. In some embodiments, the pH of the solution is adjusted to be greater than about 2 and less than about 7, greater than about 4 and less than about 7, or greater than about 4 and less than about 6. In some embodiments, adjusting the pH comprises adding a base, e.g., NaOH. In some embodiments, adjusting the pH comprises forming a buffer. In some embodiments, forming the buffer comprises adding sodium acetate.

More embodiments for methods of preparing a minocycline-containing pharmaceutical composition includes dissolving minocycline in a solution comprising a divalent or trivalent cation; and adjusting the pH of the solution to be less than 7.

In some embodiments, a solution of a 7-dimethylamino-tetracycline can be prepared by adding a 7-dimethylamino-tetracycline, an aqueous solution of divalent or trivalent salt to provide a certain divalent or trivalent salt to 7-dimethylamino-tetracycline molar ratio. The pH of the solution can be adjusted to a certain pH with a buffer, acid, or a base. The osmolality of the solution can be adjusted to a certain osmolality. The solution can be lyophilized. The lyophilized solution can be reconstituted with a diluent such as water.

In some embodiments, a solution of a 7-dimethylamino-tetracycline can be prepared by adding a 7-dimethylamino-tetracycline to an acid, such as HCl. The solution can be lyophilized. The lyophilized solution can be reconstituted with a diluent comprising a divalent or trivalent salt to provide a certain divalent or trivalent salt to 7-dimethylamino-tetracycline molar ratio. The diluent can further comprise an acid, base, or buffer, such as sodium acetate, to provide a solution of a certain pH.

In some embodiments, minocycline can be in a buffer comprising MgSO_4 at pH 5. The solution can be lyophilized. The lyophilisate can be reconstituted in an aqueous diluent. In some embodiments, minocycline can be solubilized in an aqueous solution comprising HCl, MgSO_4 and sodium acetate. The solution can be lyophilized. In some embodiments, minocycline can be solubilized in an aqueous solution comprising HCl. The solution can be lyophilized. The lyophilisate can be reconstituted in an aqueous solution. In some embodiments, the reconstituting solution can lack Mg. Kits

Some embodiments of the present invention include kits comprising a composition described herein. Some kits include a single use container comprising a composition

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described herein. Single use containers include ampules, vials, and the like. The single-use container can comprise a lyophilized formulation of a composition described herein. Some kits include a diluent for reconstituting the lyophilized formulations of a composition or pharmaceutical composition described herein.

In some embodiments, the compositions of the invention may be prepared for single-dosage use. In this embodiment, the solutions of the invention are lyophilized in individual vials such as 20-mL vials. Upon lyophilization, the vials are stoppered with any acceptable stopper. The stoppered vials are then shipped for use. When needed, the vials can be reconstituted by adding sufficient diluents to achieve the desired concentration of tetracycline. The concentration of reconstituted solutions may be easily determined by those of ordinary skill in the art. Any pharmaceutically acceptable diluent may be used. Examples of such diluents include but are not limited to water, 0.9% saline, Lactated Ringer's injection solution and dextrose solutions including 5% dextrose (5DW).

In some embodiments, the diluent does not comprise a pharmaceutically acceptable oil (e.g., polyoxyethylene hydrogenated castor oils), a pyridine-containing compound (e.g., nicotinamide), gluconate, an antioxidant, an alcohol (e.g., a polyhydric alcohol, such as, propylene glycol, ethylene glycol), glycerol, polyethylene glycol, a pyrrolidone-containing compound, a water-miscible local anaesthetic (e.g., procaine, tetracaine), urea, lactose, or a dehydrating agent (e.g., ethyl acetate, acetic anhydride, absolute ethanol, ethyl acetate, acetic anhydride, and mixtures thereof). In some embodiments, the diluent does not comprise a tetracycline-solubilizing cosolvent.

In some embodiments, the diluent contains the divalent or trivalent cation. For example, some embodiments include kits that comprise a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises minocycline in an amount such that the molar ratio of the divalent or trivalent cation to minocycline is greater than about 2:1. In some embodiments, the diluent comprises an acid, e.g., HCl. In some embodiments, the diluent comprises a buffer. In some embodiments, the buffer is sodium acetate.

More embodiments include kits comprising a first container comprising a diluent that comprises an aqueous solution of a divalent or trivalent cation; and a second container comprising a solid composition soluble in the diluent, wherein the solid composition comprises a tetracycline antibiotic in an amount such that the molar ratio of the divalent or trivalent cation to tetracycline antibiotic is greater than 3:1.

More embodiments include single use vials comprising any composition wherein the vial comprises an amount of a tetracycline of at least 100 μg , 200 μg , 300 μg , 400 μg , 500 μg , 600 μg , 700 μg , 800 μg , 900 μg , 1000 μg . In some embodiments, the vial comprises an amount of a tetracycline of at least 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, and 130 mg. In some embodiments, the vial comprises an amount of a tetracycline of at least 100 mg, 200 mg, 300 mg, 400 mg, and 500 mg. In some embodiments, the vial comprises about 100 mg of a tetracycline. In some embodiments, the tetracycline is minocycline. In some embodiments, the tetracycline is tigecycline. In some such embodiments, a vial can comprise greater than 30 mg and less than 100 mg tigecycline.

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Methods of Treatment

Some embodiments include methods of treating or preventing a bacterial infection in a subject by administering a composition described herein. "Treating," as used herein, refers to administering a pharmaceutical composition for therapeutic purposes to a patient suffering from a bacterial infection. "Preventing," as used herein, refers to treating a patient who is not yet infected, but who is susceptible to, or otherwise at risk of, a particular infection, whereby the treatment reduces the likelihood that the patient will develop an infection.

In some embodiments, the administration is via an intravenous route such as by administering an aqueous solution described herein intravenously.

Some such methods include administering an aqueous solution of minocycline and a divalent or trivalent cation to a subject via an intravenous route. Such solutions are described herein.

Some embodiments include administering an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a divalent or trivalent cation to a subject via an intravenous route, wherein the molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than about 3:1 and wherein the solution does not comprise gluconate or a pyridine-containing compound and has a pH greater than 2 and less than 7.

In some embodiments of intravenous administration, the compositions described herein permit use of lower volumes and faster infusion times due to increased concentrations of tetracycline antibiotic and reduced injection site phlebitis as compared to currently available intravenous formulations. In some embodiments, the total volume administered is less than 50 ml, less than 60 ml, less than 70 ml, less than 80 ml, less than 90 ml, less than 100 ml, less than 110 ml, less than 120 ml, less than 130 ml, less than 140 ml, less than 150 ml, less than 200 ml, less than 300 ml, less than 400 ml, less than 500 ml, or less than 1000 ml. In some embodiments, about 100 ml is administered. In some embodiments, the entire volume to be administered is administered in less than 10 minutes, less than 20 minutes, less than 30 minutes, less than 40 minutes, less than 50 minutes, less than 60 minutes, less than 70 minutes, less than 80 minutes, less than 90 minutes, less than 2 hours, less than 3 hours, or less than 4 hours. In some embodiments, the entire volume is administered in 20-70 minutes. In some embodiments, the entire volume is administered in 30-60 minutes.

Some embodiments include administering a composition described herein by a topical route. Examples of topical routes include skin, eye, ear, rectal, vaginal, urethral. Methods of such administration are well known in the art and can include aqueous solution, spray, suppository, salve, or an ointment or the like. Accordingly, some embodiments include administering an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a divalent or trivalent cation to a subject via a topical route. In some such embodiments, the molar ratio of divalent or trivalent cation to tetracycline antibiotic is greater than about 3:1. In some embodiments, the solution does not comprise gluconate or a pyridine-containing compound. In some embodiments, the solution has a pH greater than 2 and less than 7.

Other embodiments include administering a composition described herein by pulmonary inhalation. For example, compositions may be administered by inhalation of an aerosol of the composition. The aerosol may be formed using dry particles of the composition or by nebulization of a solution of suspension of the composition. Any suitable aerosolization device may be used, including dry-powder inhalers, metered-dose inhalers, and nebulizers.

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The following examples illustrate various embodiments of the invention and are not intended to limit the invention in any way.

EXAMPLES

Example 1

Stability at 37° C. for Solutions of Tigecycline or Tygacil® Containing Metal Cations

General Procedures: Some of following examples include experiments in which the stabilities of various aqueous solutions of a tetracycline were analyzed. Some solutions included a carbohydrate and/or various molar amounts of metal salts.

The pH of the solutions were adjusted with hydrochloric acid or sodium hydroxide solution. The solutions were incubated at room temperature (approximately 22° C.) or at 37° C. Incubation of solutions at 37° C. was used as a model for long-term storage of solutions.

The stabilities of various aqueous solutions of a tetracycline were analyzed using HPLC. HPLC analyses were conducted on an Agilent 1200: Column: Eclipse Plus C18 4.6×150 mm, 5 µm. Detection: UV at 248 nm. Flow rate: 1.2 mL/min. Tigecycline retention time=4.30 min. Gradient: Solvent A=0.1% trifluoroacetic acid in acetonitrile. Solvent B=0.1% trifluoroacetic acid in water. TABLE 1 shows the HPLC gradient used.

TABLE 1

Time (min)	% Solvent A	% Solvent B
0.0	5	95
9.5	50	50
10.0	5	95
15.0	5	95

A 10 mg/mL Tigecycline aqueous solution was prepared and 300 µL aliquots dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M MgCl₂, 0.1 M CaCl₂ or 0.1 M ZnCl₂ to achieve the desired molar ratio of Tigecycline:metal cation. The tubes were incubated in the dark at 37° C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

A 10 mg/mL (17.08 mol/L) aqueous solution of Tygacil® (Lot D 90293, 53 mg), a commercial Tigecycline formulation containing lactose, was prepared, and 240 µL aliquots were dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M MgCl₂, 0.1 M CaCl₂ or 0.1 M ZnCl₂ to achieve the desired molar ratio of Tigecycline:metal cation. The tubes containing the solution were incubated in the dark at 37° C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, and 7 for solutions of Tigecycline at various molar ratios with MgCl₂, CaCl₂, or ZnCl₂ are shown in TABLE 2, TABLE 3, and TABLE 4, respectively. The percentages of Tigecycline remaining at Day 0, 1, 2, 5, and 7 for solutions of Tygacil® at various ratios with MgCl₂, CaCl₂, or ZnCl₂ are shown in TABLE 5, TABLE 6, and TABLE 7, respectively.

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TABLE 2

MgCl ₂ :Tigecycline					
Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.42	98.93	97.68	92.31	85.95
5:1	99.45	98.85	97.30	88.64	81.41
2:1	99.50	98.57	96.85	84.95	73.95
1:1	99.64	98.64	96.70	82.54	67.87
0.5:1	99.60	98.45	96.52	79.39	62.20
0.2:1	99.56	98.44	95.91	72.81	53.83
0.1:1	99.50	98.29	95.66	67.28	48.68
0:1	99.53	98.23	95.18	58.42	40.90

TABLE 3

CaCl ₂ :Tigecycline					
Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.49	99.02	97.89	91.88	86.31
5:1	99.44	98.66	97.31	87.13	80.87
2:1	99.38	98.06	96.66	83.63	75.05
1:1	99.58	98.33	96.54	81.30	70.18
0.5:1	99.56	98.61	96.15	76.00	64.81
0.2:1	99.58	98.47	95.99	72.84	57.19
0.1:1	99.56	98.32	95.66	67.89	49.75
0:1	99.49	98.17	94.98	59.11	39.31

TABLE 4

ZnCl ₂ :Tigecycline					
Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.15	99.01	97.82	96.65	95.41
5:1	99.21	98.66	97.76	95.81	92.85
2:1	99.31	98.46	97.32	91.02	85.64
1:1	99.54	98.66	97.59	91.27	82.49
0.5:1	99.53	98.66	97.21	87.15	76.43
0.2:1	99.52	98.38	95.95	79.08	66.83
0.1:1	99.50	98.39	96.11	78.80	64.93
0:1	99.46	98.37	95.02	56.30	39.05

TABLE 5

MgCl ₂ :Tygacil®					
Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.61	99.38	98.97	96.51	93.52
5:1	99.47	99.46	98.83	95.38	90.55
2:1	99.49	99.32	98.72	93.20	84.03
1:1	99.63	99.38	98.55	89.21	74.30
0.5:1	99.59	99.28	98.36	86.97	68.84
0.2:1	99.54	99.26	98.43	86.41	64.91
0.1:1	99.48	99.19	98.19	72.43	44.71

TABLE 6

CaCl ₂ :Tygacil®					
Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.41	99.41	98.88	96.51	89.98
5:1	99.40	99.29	98.48	95.38	85.50
2:1	99.45	99.22	98.34	93.20	79.62
1:1	99.71	99.44	98.44	89.21	75.34

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TABLE 6-continued

CaCl ₂ :Tygacil®					
Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
0.5:1	99.53	99.16	98.32	86.97	70.45
0.2:1	99.54	99.21	98.30	86.41	63.78
0:1	99.47	99.16	98.16	72.43	42.88

TABLE 7

ZnCl ₂ :Tygacil®					
Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7
10:1	99.41	99.45	98.90	97.89	95.78
5:1	99.44	99.27	98.68	96.87	94.30
2:1	99.39	99.25	98.74	96.09	92.22
1:1	99.56	99.50	98.98	95.60	90.67
0.5:1	99.48	99.25	98.78	93.73	86.02
0.2:1	99.52	99.35	98.43	89.34	77.79
0:1	99.50	99.27	98.12	69.85	42.15

While Tigecycline decomposed in all tubes over 7 days, the rate of decomposition was significantly lower in solutions containing higher molar ratios of metal cation. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar; however, the rate of Tigecycline decomposition in the presence of zinc was significantly lower. The presence of lactose in the Tygacil® formulation further decreased the rate of decomposition.

Example 2

Stability at Room Temperature for Solutions of Tigecycline or Tygacil® Containing Metal Cations

A 10 mg/mL Tigecycline aqueous solution was prepared and 240 µL aliquots dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M MgCl₂, 0.1 M CaCl₂ or 0.1 M ZnCl₂ to achieve the desired molar ratio of Tigecycline:metal cation. The tubes were incubated in the dark at 37° C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 240 µL aliquots were dispensed into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 0.1 M MgCl₂, 0.1 M CaCl₂ or 0.1 M ZnCl₂ to achieve the desired molar ratio of Tigecycline:metal cation. The tubes were incubated in the dark at 37° C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, 21, 28, and 36 for solutions of Tigecycline at various molar ratios with MgCl₂, CaCl₂, or ZnCl₂ are shown in TABLE 8, TABLE 9, and TABLE 10, respectively. The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, 21, 28, and 36 for solutions of Tygacil® at various ratios with MgCl₂, CaCl₂, or ZnCl₂ are shown in TABLE 11, TABLE 12, and TABLE 13, respectively.

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TABLE 8

MgCl ₂ :Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.58	99.32	99.46	99.03	98.62	95.52	91.90	85.33	76.89
5:1	99.45	99.32	99.41	98.74	98.16	94.04	87.10	76.71	62.60
2:1	99.51	99.27	99.43	98.46	96.97	89.87	76.29	58.07	40.67
1:1	99.66	99.45	99.36	98.35	96.49	85.88	66.59	46.07	31.90
0.5:1	99.64	99.40	99.35	97.76	96.16	81.98	59.70	39.79	28.16
0.2:1	99.56	99.37	99.28	97.93	95.45	75.81	50.38	34.00	24.19
0:1	99.46	99.24	99.15	97.01	94.08	61.98	38.99	24.55	16.33

TABLE 9

CaCl ₂ :Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.58	99.34	99.41	99.05	98.59	95.45	92.00	86.92	82.47
5:1	99.48	99.25	99.27	98.66	98.13	93.61	88.60	81.75	74.95
2:1	99.37	99.27	99.25	98.03	97.16	91.36	82.92	72.83	62.43
1:1	99.57	99.38	99.30	98.53	96.92	89.14	78.35	65.46	53.22
0.5:1	99.59	99.30	99.30	98.32	96.54	86.26	72.73	58.20	45.11
0.2:1	99.48	99.32	99.27	97.94	95.75	80.39	61.83	45.47	26.69
0:1	99.44	99.29	99.17	96.76	93.75	60.72	38.08	23.94	15.72

TABLE 10

ZnCl ₂ :Tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.24	98.99	99.49	99.30	99.19	97.49	97.63	96.09	94.32
5:1	99.29	99.13	99.05	99.27	99.16	97.40	95.98	92.80	90.60
2:1	99.34	99.23	99.51	99.06	98.82	95.79	93.63	86.84	80.66
1:1	99.53	99.39	99.47	99.03	98.48	94.61	88.48	79.03	69.44
0.5:1	99.50	99.39	99.33	98.76	96.77	90.07	78.03	65.63	54.07
0.2:1	99.46	99.37	99.33	98.24	96.50	85.72	69.89	55.13	41.97
0:1	99.44	99.39	99.12	97.28	93.31	59.45	37.09	23.57	15.48

TABLE 11

MgCl ₂ :Tygacil ® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.44	99.53	99.34	99.25	99.07	97.30	95.37	92.20	86.32
5:1	99.44	99.61	99.60	99.45	99.32	97.66	95.34	90.98	83.58
2:1	99.48	99.63	99.56	99.43	99.19	96.67	91.94	81.95	66.57
1:1	99.55	99.62	99.61	99.09	99.11	96.50	89.71	74.36	55.95
0.5:1	99.49	99.64	99.60	99.33	98.70	95.10	84.39	64.70	45.04
0.2:1	99.49	99.63	99.57	99.28	98.89	94.03	79.53	57.09	37.94
0:1	99.44	99.57	99.57	99.25	98.78	89.19	65.09	42.56	28.38

TABLE 12

CaCl ₂ :Tygacil ® Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	99.32	99.51	99.45	99.50	99.26	97.41	95.08	92.06	87.88
5:1	99.35	99.51	—	99.33	99.02	97.36	93.42	88.57	82.75
2:1	99.40	99.67	99.46	99.25	98.97	95.76	90.00	81.77	72.75
1:1	99.49	99.60	99.54	99.39	99.02	95.44	88.25	77.42	65.65
0.5:1	99.48	99.60	99.49	99.30	98.55	94.80	85.57	71.96	58.07
0.2:1	99.44	99.57	99.53	99.27	98.89	92.70	80.03	62.28	47.05
0:1	99.45	99.60	99.55	99.18	98.70	88.02	63.58	40.77	28.00

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TABLE 13

ZnCl ₂ :Tygacil ®									
Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21	Day 28	Day 36
10:1	98.91	99.49	99.43	99.46	99.47	98.98	98.68	98.17	98.11
5:1	99.15	99.54	99.51	99.45	99.35	98.88	98.26	97.39	96.15
2:1	99.29	99.57	99.55	99.35	99.37	98.60	97.42	95.30	92.37
1:1	99.44	99.62	99.55	99.61	99.33	97.97	96.29	92.70	87.08
0.5:1	99.47	99.62	99.59	99.48	99.25	97.60	94.10	86.46	76.49
0.2:1	99.45	99.62	99.61	99.47	99.19	96.09	89.52	77.46	63.06
0:1	99.42	99.54	99.52	99.14	98.71	88.25	64.08	41.19	28.09

While Tigecycline decomposed in all tubes over 36 days, the rate of decomposition was significantly lower in solutions containing higher molar ratios of metal cation. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar; however, the rate of Tigecycline decomposition in the presence of zinc was significantly lower. The presence of lactose in the Tygacil® formulation further decreased the rate of decomposition.

Example 3

Stability at 37° C. for Tygacil Solutions Containing High Concentrations of Metal Cations

A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 300 µL aliquots were dispensed

into polypropylene tubes. The volume of each tube was adjusted to 1 ml with various dilutions of 1 M MgCl₂, 1 M CaCl₂ or 1 M ZnCl₂ to achieve the desired molar ratio of Tigecycline:metal cation. The tubes were incubated in the dark at 37° C. Samples of each solution were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, and 21 for solutions of Tygacil® at various ratios with MgCl₂, CaCl₂, or ZnCl₂ are shown in TABLE 14, TABLE 15, and TABLE 16, respectively.

TABLE 14

MgCl ₂ :Tygacil ®							
Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
30:1	99.64	99.59	99.49	98.54	97.11	89.62	77.13
20:1	99.61	99.56	99.23	97.99	95.94	85.04	63.47
12:1	99.58	99.53	99.14	96.74	94.45	77.71	46.81
5:1	99.68	99.56	99.6	96.06	91.18	59.13	25.95
0:1	99.65	99.23	98.26	75.05	46.66	6.37	1.30

TABLE 15

CaCl ₂ :Tygacil ®							
Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
30:1	99.58	99.55	99.29	97.79	95.9	86.94	69.71
20:1	99.62	99.51	99.18	97.00	93.81	80.6	55.28
12:1	99.60	99.41	98.94	94.94	91.13	69.3	40.59
5:1	99.65	99.42	98.66	92.83	85.72	53.1	24.74
0:1	99.60	99.34	98.25	74.61	45.63	6.26	1.53

TABLE 16

ZnCl ₂ :Tygacil ®							
Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
12:1	99.44	99.27	99.49	98.60	97.66	92.50	83.58
5:1	99.48	—	99.22	97.42	96.21	87.22	71.55
0:1	99.62	—	98.22	73.43	43.3	6.37	1.57

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While Tigecycline decomposed in all tubes over 21 days, the rate of decomposition was significantly lower in solutions containing higher molar ratios of metal cation. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar, however, the rate of Tigecycline decomposition in the presence of zinc was significantly lower.

Example 4

Effect of pH on the Stability of Tygacil® Solutions Containing Metal Cations at 37° C.

A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 16504 aliquots were dispensed into four 15 mL polypropylene tubes. The volume of each tube was adjusted to 5500 µL with various dilutions of 0.1 M MgCl₂, 0.1 M CaCl₂, or 0.1 M ZnCl₂, or water (control), to achieve the desired molar ratio of a 1:1 ratio of Tigecycline: metal cation. Sample solutions from each 15 ml tube were taken and adjusted to pH 4, 5, or 6 with 0.1 N or 1 N solutions of NaOH or HCl, taking care to minimize volume changes. Samples solutions were incubated in the dark at 37° C. Samples were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline (expressed as a percentage of the starting concentration) in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions of Tygacil® at 1:1 ratios with MgCl₂, CaCl₂, or ZnCl₂ at various pHs are shown in TABLE 17, TABLE 18, and TABLE 19, respectively. TABLE 20 shows percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions of Tygacil® only at various pHs

TABLE 17

pH for 1:1 MgCl ₂ :Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.51	98.89	98.89	95.72	90.92	54.54
pH 5	99.55	99.09	98.00	84.77	63.60	15.89
pH 6	99.53	98.36	95.79	44.81	23.71	5.19

TABLE 18

pH for 1:1 CaCl ₂ :Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.49	98.88	98.84	94.43	90.06	55.91
pH 5	99.66	99.02	97.8	81.96	69.23	28.89
pH 6	99.62	98.70	97.87	92.45	87.40	56.79

TABLE 19

pH for 1:1 ZnCl ₂ : Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.47	98.62	99.03	96.14	93.15	73.25
pH 5	99.6	99.21	98.96	93.02	83.48	39.93
pH 6	99.54	99.3	99.16	94.58	86.35	49.21

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TABLE 20

pH for Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.48	99.07	98.93	94.28	87.05	44.75
pH 5	99.6	98.94	96.89	49.21	27.49	2.16
pH 6	99.47	95.27	59.56	10.74	2.4	5.22

While Tigecycline decomposed in all tubes over 14 days, the rate of decomposition was significantly lower in solutions with a pH lower than pH 6. The rates of Tigecycline decomposition in the presence of calcium or magnesium cations were similar at pH 4 and 5; however, the rate of Tigecycline decomposition in the presence of magnesium at pH 6 was significantly greater. The rate of Tigecycline decomposition at pH 4 and 5 in solutions containing zinc was lower than solutions containing magnesium or calcium. The rates of Tigecycline decomposition at pH 6, in solutions containing zinc or calcium were similar. The rate of Tigecycline decomposition at all pHs was much lower in the presence of metal cations, especially at higher pH.

Example 5

Effect of pH on the Stability of Tygacil® Solutions Containing High Concentrations of Metal Cations at 37° C.

A 10 mg/mL aqueous solution of Tygacil® (Lot D 90293, 53 mg) was prepared, and 1650 µL aliquots were dispensed into four 15 mL polypropylene tubes. The volume of each tube was adjusted to 5500 µL with various dilutions of 1 M MgCl₂, 1 M CaCl₂, or 1 M ZnCl₂, or water (control), to achieve the desired molar ratio of a 1:12 ratio of Tigecycline: metal cation. Sample solutions from each 15 ml tube were taken and adjusted to pH 4, 5, or 6 with 0.1 N or 1 N solutions of NaOH or HCl, taking care to minimize volume changes. Samples solutions were incubated in the dark at 37° C. Samples were taken at various time points and analyzed by HPLC. The fraction of remaining Tigecycline in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions of Tygacil® at 1:12 ratios with MgCl₂, CaCl₂, or ZnCl₂ at various pHs are shown in TABLE 21, TABLE 22, and TABLE 23, respectively.

TABLE 21

pH for 12:1 MgCl ₂ : Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.47	98.62	99.18	97.49	95.72	83.14
pH 5	99.61	98.87	99.12	96.53	93.72	69.08
pH 6	99.58	99.26	99.21	95.6	96.96	85.86

TABLE 22

pH for 12:1 CaCl ₂ : Tygacil®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.48	97.24	98.89	96.01	92.85	73.05
pH 5	99.74	99.36	99.41	97.64	95.94	89
pH 6	99.61	99.44	99.48	98	97.09	92.18

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TABLE 23

pH for 12:1 ZnCl ₂ : Tygacil ®	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	99.49	99.29	99.36	98.73	98.35	95.19
pH 5	99.56	99.47	99.47	98.38	98.04	93.38
pH 6	99.65	99.38	99.49	98.78	98.79	97.67

While tigecycline decomposed in all tubes over 14 days, the rate of decomposition was slower in solutions at pH 6. The rates of Tigecycline decomposition in the presence of calcium were slower in solutions at greater pH. When formulated as Tygacil, the rates of tigecycline decomposition in the presence of zinc or magnesium were faster at pH 5.

Example 6

Effect of pH on the Stability of Minocycline
Solutions Containing High Concentrations of MgCl₂
at 37° C.

A 10 mg/mL Minocycline hydrochloride aqueous solution was prepared, and 2500 µL aliquots were dispensed into two 15 mL polypropylene tubes. The volume of each tube was adjusted to 5500 µL with either a dilution of 1 M MgCl₂ to achieve a molar ratio of a 1:10 ratio of Minocycline:metal cation, or water. Sample solutions from each 15 ml tube were taken and adjusted to pH 4, 5, or 6 with 0.1 N or 1 N solutions of NaOH or HCl, taking care to minimize volume changes. Sample solutions were incubated in the dark at 37° C. Samples were taken at various time points and analyzed by HPLC. The fraction of minocycline remaining in each sample was determined.

The percentages of Minocycline remaining at Day 0, 1, 2, 5, 7, and 14 for solutions at various pHs of Minocycline at 1:10 ratio with MgCl₂, or Minocycline solutions alone are shown in TABLE 24, and TABLE 25, respectively.

TABLE 24

pH for 10:1 MgCl ₂ : Minocycline	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	98.63	96.97	96.46	94.76	93.43	84.32
pH 5	98.69	97.05	96.19	93.01	89.31	75.42
pH 6	99.03	97.1	96.04	88.45	83.88	76.25

TABLE 25

pH for Minocycline alone	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14
pH 4	98.75	96.37	96.21	94.99	92.78	81.82
pH 5	98.41	96.72	95.29	85.01	75.14	35.43
pH 6	98.19	95.47	87.55	39.17	14.56	2.2

While Minocycline decomposed in all tubes over 14 days, the rate of decomposition was significantly lower in solutions containing magnesium, especially at higher pH.

Example 7

Stability of Tigecycline Solutions Containing
Mixtures of CaCl₂ and MgCl₂ at pH 6 and 37° C.

A 10 mg/mL aqueous solution of Tigecycline was prepared, and 450 µL aliquots were dispensed into 15 mL

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polypropylene tubes. The volume of each tube was adjusted to 1500 µL with various dilutions of 1 M MgCl₂ and 1 M CaCl₂, or water (control), to achieve the desired molar ratios of Tigecycline:metal cation. Sample solutions from each 15 ml tube were taken and adjusted to pH 6 with 0.1 N or 1 N solutions of NaOH or HCl, taking care to minimize volume changes. Samples solutions were incubated in the dark at 37° C. Samples were taken at various time points and analyzed by HPLC. The fraction of Tigecycline remaining in each sample was determined.

The percentages of Tigecycline remaining at Day 0, 1, 2, 5, 7, 14, and 21 for solutions of at various ratios of Tigecycline: MgCl₂:CaCl₂ at pH 6 are shown in TABLE 26.

TABLE 26

MgCl ₂ :CaCl ₂ : tigecycline Molar ratio	Day 0	Day 1	Day 2	Day 5	Day 7	Day 14	Day 21
5:5:1	98.25	98.77	98.23	96.91	92.13	83.64	65.21
5:10:1	98.37	98.23	98.59	97.76	96.10	89.74	79.83
10:5:1	98.17	98.21	98.46	96.59	93.90	80.00	59.39
10:10:1	98.32	98.24	98.50	97.38	95.62	87.14	72.88
5:0:1	98.18	97.93	97.53	90.58	76.71	40.42	12.54
10:0:1	98.16	98.00	98.23	94.91	89.12	62.54	35.75
15:0:1	98.25	98.13	98.21	96.23	92.32	72.15	48.75
20:0:1	98.2	98.08	98.28	96.46	93.72	78.66	57.66
0:5:1	98.11	98.15	98.28	97.19	95.68	89.2	77.2
0:10:1	98.12	98.2	98.55	97.1	96.53	91.74	84.69
0:15:1	98.15	98.21	98.59	97.5	96.93	92.71	86.37
0:20:1	98.28	98.63	98.57	97.4	97.35	93.09	87.45
0:0:1	97.91	88.97	60.59	16.36	7.33	4.14	0

While Tigecycline decomposed in all tubes over 21 days, the rate of decomposition was significantly lower in solutions containing greater relative amounts of calcium cations.

Example 8

Effects of MgCl₂ on Minocycline-Induced Hemolysis
in an In Vitro Model of Venous Phlebitis

In vitro hemolysis of rabbit red blood cells (RBCs) after exposure to minocycline formulated in MgCl₂ or CaCl₂ was compared to in vitro hemolysis of RBCs after exposure to minocycline in saline, or exposure to amphotericin B. Minocycline HCl (LKT laboratories) stock solutions were prepared with MgCl₂ in saline, or lactated ringer, and the pH was adjusted with NaOH. Rabbit and sheep red blood cells (RBCs) were obtained from Innovative Research laboratory (Michigan, USA). Immediately before use, RBCs were washed three times in 0.9% saline and adjusted to a density of 5% in saline. 200 µL RBCs was added to 800 µL minocycline solution, and mixed by gentle inversion for 2-5 seconds. Samples were incubated at 37° C. or 30 minutes or at 25° C. for 2-5 minutes. Incubated samples were centrifuged at 12000xg for 4 minutes and the supernatants were removed and the hemoglobin absorbance was read at 540 nm. Samples were tested in triplicate. Amphotericin B (MP Biomedicals) and distilled H₂O, or Triton-x and distilled H₂O were used as positive controls; saline was used as a negative control. Percent hemolysis was calculated according to the following formula:

Percent hemolysis=

$$\frac{(\text{absorbance of sample}) - (\text{absorbance of blank})}{\text{Absorbance of Distilled H}_2\text{O}} \times 100$$

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In a set of experiments, the pH of minocycline solutions formulated with divalent cations was adjusted to pH 5.85. For RBCs incubated in aminocycline saline solution, hemolysis was in the range of 44%-84% (FIG. 1). For RBCs incubated in aminocycline with Mg^{2+} or Ca^{2+} , hemolysis was approximately 2%. Results summarizing the percent in vitro hemolysis of rabbit RBCs incubated with different formulations of minocycline or amphoterin B at 25° C. are summarized in Table 27.

TABLE 27

Solution	Hemolysis of RBCs in solution relative to water (%)
5 mg/ml minocycline, 10 equiv Mg, pH 5.85	2.8
2.5 mg/ml minocycline, 10 equiv Mg, pH 5.85	3.2
0.5 mg/ml minocycline, 10 equiv Mg, pH 5.85	2.3
5 mg/ml minocycline, 5 equiv Ca, pH 5.85	2.2
2.5 mg/ml minocycline, 5 equiv Ca, pH 5.85	2.94
0.5 mg/ml minocycline, 5 equiv Ca, pH 5.85	2.20
5 mg/ml minocycline, saline, pH 4.17	81.64
2.5 mg/ml minocycline, saline, pH 4.17	84.37
0.5 mg/ml minocycline, saline, pH 4.17	43.82
Amphoterin B	101.31

In another set of experiments, the pH of aminocycline solution formulated with divalent cations was not adjusted and was allowed to fall below the pH of minocycline in saline. For RBCs incubated in aminocycline saline solution, hemolysis was in the range of 44%-84% (FIG. 2). For RBCs incubated in aminocycline with Mg^{2+} or Ca^{2+} , hemolysis was in the range of 0%-5%. Results summarizing the percent in vitro hemolysis of rabbit RBCs incubated with different formulations of minocycline at low pH, or amphoterin B at 25° C. are summarized in Table 28.

TABLE 28

Solution	Hemolysis of RBCs in solution relative to water (%)
5 mg/ml minocycline, 10 equiv Mg, pH 3.5	0.88
2.5 mg/ml minocycline, 10 equiv Mg, pH 3.5	1.12
0.5 mg/ml minocycline, 10 equiv Mg, pH 3.5	2.20
5 mg/ml minocycline, 5 equiv Ca, pH 3.64	—
2.5 mg/ml minocycline, 5 equiv Ca, pH 3.64	0.86
0.5 mg/ml minocycline, 5 equiv Ca, pH 3.64	4.92
5 mg/ml minocycline, saline, pH 4.17	81.64
2.5 mg/ml minocycline, saline, pH 4.17	84.37
0.5 mg/ml minocycline, saline, pH 4.17	43.82
Amphoterin B	101.31

Hemolysis of RBCs was reduced in an in vitro model of venous phlebitis with minocycline solutions formulated with divalent cations compared to minocycline solutions formulated without divalent cations.

In another set of experiments, hemolysis of rabbit RBCs was measured after exposure to 2.5 mg/ml minocycline formulated with different ratios of divalent cations ($MgCl_2$, $MgSO_4$, or $CaCl_2$). Hemolysis was compared to Minocycline HCl. Triton-x and H_2O were used as positive controls. Results are summarized in Table 29 and shown in FIGS. 4-6.

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TABLE 29

2.5 mg/ml minocycline solution		Hemolysis of RBCs
Cation	Molar ratio cation:minocycline	in solution relative to water (%)
$MgSO_4$	1:2	22.52
	1:1	24.59
	2:1	40.87
	3:1	25.67
	5:1	2.86
	7:1	1.96
	10:1	0.19
$MgCl_2$	1:2	46.91
	1:1	63.77
	2:1	74.87
	3:1	64.62
	5:1	9.43
	7:1	1.57
	10:1	0.35
$CaCl_2$	1:2	75.22
	1:1	83.89
	2:1	50.84
	3:1	26.58
	5:1	1.16
	7:1	0.75
	10:1	0.40
Minocycline only		37.44
Triton-x		97.82

FIG. 3 and FIG. 4 show the degree of rabbit RBC hemolysis produced by minocycline formulated in different ratios of $MgSO_4$ or $MgCl_2$, respectively, compared to Minocycline only. The data indicates that a 5:1 molar ratio of magnesium to minocycline or greater inhibits the RBC hemolysis observed with minocycline alone. Minocycline (minocin) produced a relative RBC hemolysis of 37%. FIG. 5 shows the degree of rabbit RBC hemolysis produced by minocycline formulated in different ratios of $CaCl_2$. This data shows that a 5:1 molar ratio of calcium to minocycline inhibits the RBC hemolysis observed with minocycline HCl alone.

Overall, these data all suggest that high molar ratios (e.g., a 5:1 molar ratio or greater) of divalent cation (Mg^{+2} or Ca^{+2}) to minocycline results in significant inhibition of rabbit RBC hemolysis observed with minocycline HCl.

Example 9

Solubility of Minocycline with Divalent Cations

Mixtures were prepared containing minocycline and divalent cations (Mg^{2+} or Ca^{2+}) at varying stoichiometry and pH. The solubility of minocycline was assessed according to the turbidity of the mixture at 0 hr, 24 hr, 48 hr, 72 hr, 96 hr, 120 hr, 144 hr, and 168 hr. A clear solution denoted complete solubility. Table 30 summarizes data for minocycline with Mg^{2+} at 0 hr and 24 hr. Table 31 summarizes data for minocycline with Ca^{2+} at 0 hr and 24 hr.

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TABLE 30

		Molar ratio cation (Mg ²⁺): minocycline															
		0		1:2		1:1		2:1		3:1		5:1		7:1		10:1	
		Time (hr)															
		0	24	0	24	0	24	0	24	0	24	0	24	0	24	0	24
1 mg/ml minocycline	pH 4	○	○											○	○	○	○
	pH 5	○	○											○	○	○	○
	pH 6	○	○											○	○	○	○
	pH 7	○	○											○	○	○	○
5 mg/ml minocycline	pH 4	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 6	○	○	●	●	●	●	●	●	●	●	○	●	○	●	○	○
10 mg/ml minocycline	pH 4	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	○	○	●	○	●	○	●	○	○	○	○	○	○
	pH 6	○	○	●	●	●	●	●	●	●	●	○	●	○	●	○	○
20 mg/ml minocycline	pH 4	○	●										○	○	○	○	○
	pH 5	○	○										○	●	○	○	●
30 mg/ml minocycline	pH 4	○	●										○	○	○	○	○
	pH 5	○	●										○	○	○	○	●

●: insoluble;
○: soluble

●: insoluble;
○: soluble

TABLE 31

		Molar ratio cation (Ca ²⁺): minocycline															
		0		1:2		1:1		2:1		3:1		5:1		7:1		10:1	
		Time (hr)															
		0	24	0	24	0	24	0	24	0	24	0	24	0	24	0	24
1 mg/ml minocycline	pH 4	○	○										○	○	○	○	○
	pH 5	○	○										○	○	○	○	○
	pH 6	○	○										○	○	○	○	○
	pH 7	○	○										○	●	○	●	○
5 mg/ml minocycline	pH 4	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 6	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○
10 mg/ml minocycline	pH 4	○	○	○	○	○	○										
	pH 5	○	○	○	○	○	○										
	pH 6	○	○	○	○	○	○										
20 mg/ml minocycline	pH 4	○	●										○	○	○	○	○
	pH 5	○	○										○	○	○	○	○
30 mg/ml minocycline	pH 4	○	●										○	●	○	○	●
	pH 5	○	●										○	○	○	○	○

●: insoluble;
○: soluble

●: insoluble;
○: soluble

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The data demonstrates that minocycline stays in solution upon introduction of a cation at concentrations of 10 mg/ml and less if the pH is less than 5. At higher pH, introduction of a cation initially reduces solubility. For example, a 5 mg/ml minocycline solution at pH 6 becomes insoluble on addition of Mg^{2+} . Surprisingly, at a molar ratio of cation:minocycline

of 5:1 or more, the minocycline of such solutions becomes soluble, suggesting that high ratios of cation increases the solubility of minocycline.

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Table 32 summarizes data for minocycline with Mg^{2+} at 48 hr and 72 hr.

TABLE 32

		Molar ratio cation (Mg ²⁺): minocycline															
		0		1:2		1:1		2:1		3:1		5:1		7:1		10:1	
		Time (hr)															
		48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72
1 mg/ml minocycline	pH 4	○	○									○	○	○	○	○	○
	pH 5	○	○									○	○	○	○	○	○
	pH 6	○	○									○	○	○	○	○	○
	pH 7	○	○									○	○	○	○	○	○
5 mg/ml minocycline	pH 4	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○
	pH 6	○	○	●	●	●	●	●	●	●	●	●	●	●	●	○	●

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TABLE 32-continued

		Molar ratio cation (Mg ²⁺): minocycline															
		0		1:2		1:1		2:1		3:1		5:1		7:1		10:1	
		Time (hr)															
		48	72	48	72	48	72	48	72	48	72	48	72	48	72	48	72
10 mg/ml minocycline	pH 4	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	pH 5	●	●	○	●	●	●	●	●	●	●	○	●	○	●	○	○
	pH 6	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
20 mg/ml minocycline	pH 4	●	●									○	○	○	○	○	○
	pH 5	●	●									●	●	●	●	●	●
30 mg/ml minocycline	pH 4	●	●									○	○	○	○	○	○
	pH 5	●	●									●	●	●	●	●	●

●: insoluble;
○: soluble

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Example 10

Long-Term Stability of Tigecycline at Various Temperatures

Table 33, Table 34, and Table 35 show percentage remaining tigecycline for different formulations of tigecycline at pH 6, stored at 37° C., room temperature, and 4° C., respectively. Formulations of tigecycline comprising increasing concentrations of tigecycline and increasing concentrations of CaCl₂ showed increased stability.

TABLE 33

Formulation		Stability of tigecycline (%)					
		0 day	1 day	2 days	5 days	7 days	14 days
Salt	stored at 37° C.						
MgCl ₂	12 eq 20 mg/mL	97.97	97.43	96.37	92.63	88.41	
	5 eq 20 mg/mL	98.09	97.38	96.42	88.64	81.62	
	2 eq 20 mg/mL	97.95	97.28	94.1	80.59	69.88	
	12 eq 3 mg/mL	98.17	98.05	97.08	93.78	88.16	
	5 eq 3 mg/mL	98.3	97.72	96.77	86.97	73.76	
	2 eq 3 mg/mL	98.21	97.22	93.75	62.21	45.31	
	12 eq 20 mg/mL	98.3	98	97.63	96.1	95.24	91.44
	5 eq 20 mg/mL	98.16	97.75	97.4	95.82	94.81	89.26
CaCl ₂	2 eq 20 mg/mL	98.25	97.85	97.22	95.28	93.64	88.61
	12 eq 3 mg/mL	98.29	98.03	97.74	96.79	95.92	91.07
	5 eq 3 mg/mL	98.21	97.96	97.32	95.37	94.42	86.36
	2 eq 3 mg/mL	98.17	97.74	96.57	92.99	90.22	
ZnCl ₂	1 eq 20 mg/mL	98.26	97.19	93.86	81.02	72.41	
	1 eq 3 mg/mL	98.29	97.88	96.73	86.5	74.32	

TABLE 34

Formulation stored at room		Stability of tigecycline (%)					
		0 day	7 days	14 days	28 days	42 days	58 days
Salt	tem- perature						
MgCl ₂	12 eq 20 mg/mL	97.97	96.56	93.4	79.44		
	5 eq 20 mg/mL	98.09	94.2	82.17			
	2 eq 20 mg/mL	97.95	87.57	67.91			
	12 eq 3 mg/mL	98.17	97.22	94.91	80.14		
	5 eq 3 mg/mL	98.3	96.45	89.91			
	2 eq 3 mg/mL	98.21	92.66	66.91			
CaCl ₂	12 eq 20 mg/mL	98.3	97.91	97.36	95.69	95.32	93.02
	5 eq 20 mg/mL	98.16	97.88	97.23	95.24	94.08	90.78
	2 eq 20 mg/mL	98.25	97.97	97.08	94.42	93.08	87.95
	12 eq 3 mg/mL	98.29	98.01	97.7	96.37	95.78	93.67
	5 eq 3 mg/mL	98.21	97.84	97.29	95.39	94.22	90.37
	2 eq 3 mg/mL	98.17	97.53	96.47	92.85	90.07	79.52
ZnCl ₂	1 eq 20 mg/mL	98.26	82.44	65.73			
	1 eq 3 mg/mL	98.29	97.11	93.1			

TABLE 35

Formulation		Stability of tigecycline (%)					
		0 day	14 day	28 days	35 days	58 days	162 days
Salt	stored at 4° C.						
MgCl ₂	12 eq 20 mg/mL	97.97	97.68	96.16	95.36	89.95	
	5 eq 20 mg/mL	98.09	96.22	78.05	69.76		
	2 eq 20 mg/mL	97.95	91.23	54.38	43.33		
	12 eq 3 mg/mL	98.17	97.76	95.76	94.19	80.31	

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TABLE 35-continued

Salt	Formulation stored at 4° C.	Stability of tigecycline (%)					
		0 day	14 day	28 days	35 days	58 days	162 days
CaCl ₂	5 eq 3 mg/mL	98.3	97.48	91.75	86.21		
	2 eq 3 mg/mL	98.21	96.23	84.6	76.81		
	12 eq 20 mg/mL	98.3	98.28	97.78	97.61	97.87	96.4
	5 eq 20 mg/mL	98.16	97.97	97.65	97.79	97.78	95.22
	2 eq 20 mg/mL	98.25	98.08	97.69	97.8	97.75	94.9
	12 eq 3 mg/mL	98.29	98.37	98.16	97.79	98.15	97.27
	5 eq 3 mg/mL	98.21	98.17	97.97	97.76	97.99	96.75
	2 eq 3 mg/mL	98.17	98.14	97.45	97.53	97.56	93.35
ZnCl ₂	1 eq 20 mg/mL	98.26	77.12	53.06	45.63		
	1 eq 3 mg/mL	98.29	97.73	96.38	95.02	88.53	

Example 11

Solubility of Tetracycline Formulations

The solubility of four non-dimethylamino tetracyclines, with and without Mg²⁺, was examined. The results are summarized in Table 36.

TABLE 36

		Molar ratio cation (Mg ²⁺): antibiotic							
		0	0.5:1	1:1	2:1	3:1	5:1	7:1	10:1
10 mg/ml tetracycline	pH 4	●	●	●	●	●	●	●	●
	pH 5	●	●	●	●	●	●	●	●
	pH 6	●	●	●	●	●	●	●	●
10 mg/ml chlortetracycline	pH 4	●					○	○	○
	pH 5	●					●	●	●
	pH 6	●					●	●	●
10 mg/ml doxycycline	pH 4	○					●	●	●
	pH 5	○					●	●	●
	pH 6						○#	○#	○#
10 mg/ml oxytetracycline	pH 4	●					●	●	●
	pH 5	●					●	○	○
	pH 5	●					●	○	○

●: insoluble;

○: soluble;

#fell out of solution after 24 hrs at room temperature

A comparison with the results for minocycline described in Example 9 indicates that non-dimethylamino-tetracyclines, such as tetracycline, chlortetracycline, doxycycline, and oxytetracycline have solubility characteristics that differ from dimethylamino-tetracyclines. For example, as summarized in Table 36, tetracycline remains insoluble at various pH and amounts of a divalent cation such as Mg²⁺. Chlortetracycline becomes soluble with increasing concentrations of a divalent cation, but remains insoluble in the absence of any divalent cation, such as Mg²⁺. Doxycycline is soluble in the absence of divalent cations, such as Mg²⁺, but is insoluble in the presence of divalent cations at low pH. Similarly, oxytetracycline remains insoluble in the presence of divalent cations, such as Mg²⁺, at low pH.

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Example 12

Study of the Effect of Mg²⁺ on the Uptake of Minocycline in Human Umbilical Vein Endothelial Cells (HUVEC)

Cells and reagents: Human umbilical vein endothelial cells (HUVEC) were purchased from Lonza and maintained according to manufacturer's recommendations in EGM-2 media. A 10 mg/mL solution of minocycline was prepared in 13.6 mg/mL Na-acetate without addition of Mg. This stock solution was further diluted in saline to 1 mg/mL with addition of Mg in the form of 1 M MgSO₄ to generate the following molar ratios of Mg to minocycline: 0, 1, 2.5, 5, 10, 25.

Uptake experimental conditions: HUVECs were seeded at 4.5×10⁵ cells/well density in 6-well plates in EGM-2 media. Two days after seeding, cells were washed once with 2 mL of saline, and then 2 mL of 1 mg/mL drug solution in saline prepared as described above was placed in each well in triplicate. Plates were incubated in a CO₂ incubator at 37° C. for 30 min. Drug solutions were aspirated and cells were washed once with 2 mL of saline. 0.5 mL of saline was placed in each well and the cell monolayer was scraped using a plastic cell scraper. Cell suspensions were transferred to 1.5 mL plastic tubes and sonicated for 30 sec at maximal power. Cell lysates were spun down for 10 min on a table top microcentrifuge at maximum speed and supernatants were collected. Several wells of HUVEC cells were treated with saline only and processed the same way as drug-treated cells to generate mock cell lysate which was used below for calibration curve preparation.

Sample preparation for LCMS analysis: To prepare a calibration curve, 1 mg/mL minocycline solution in water was diluted in mock cell lysate to produce 100 µl of standards with the following concentrations: 10, 5, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.02, 0.01 µg/mL.

50 µl of supernatants from drug-treated samples or standards were mixed with 200 µl of 1% trifluoroacetic acid in acetonitrile containing 1 µg/mL of gatifloxacin, vortexed and centrifuged at 3000 g for 30 min at RT. 150 µl of supernatants was removed and mixed with 450 µl of water. After vortexing, the mixture was centrifuged at 3000 g for 5 min at RT. Supernatants were collected and subjected to LCMS analysis to determine minocycline concentration.

Data processing: Uptake data were presented as percentage relative to the sample with no Mg present, which was considered as 100%.

Uptake of minocycline at 1 mg/mL in saline with various Mg/minocycline ratios was tested in HUVEC with an incubation time was 30 min. The results are summarized in FIG. 6 and FIG. 7. FIGS. 6 and 7 demonstrate that a decrease in intracellular uptake of minocycline is observed as the concentration of a divalent cation, such as Mg²⁺ increases. While not being bound by any particular theory, this result suggests that the mechanism for the reduction in hemolysis observed in the minocycline/cation formulations described herein may be attributed to reduced RBC uptake.

Example 13

Preparing Certain Formulations of Dimethylamino-Tetracyclines

Formulation 1

A formulation comprising minocycline with MgCl₂ and NaOH suitable for intravenous administration is prepared. 100 mg minocycline is added to a 10 ml aqueous solution of

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MgCl₂·6H₂O to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/ml minocycline solution. The pH of the mixture is adjusted by adding NaOH to a pH in the range of pH 4.5-pH 5.5. A single attempt of lyophilization resulted in a non-flocculent solid.

Formulation 2

A formulation comprising minocycline with MgSO₄ and sodium acetate suitable for intravenous administration is prepared. 100 mg minocycline is added to an aqueous solution of MgSO₄·7H₂O to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/ml minocycline solution. The pH of the solution is adjusted by adding sodium acetate to a pH in the range of pH 4.5-pH 5.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 4.5-pH 5.5 and an osmolality in the range of 275 mOsm/kg-375 mOsm/kg.

Formulation 3

A formulation comprising minocycline with Mg(C₂H₃O₂)₂ suitable for intravenous administration is prepared. 100 mg minocycline is added to an aqueous solution of Mg(C₂H₃O₂)₂·3H₂O to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/ml minocycline solution. The solution is then lyophilized to dryness.

Formulation 4

A formulation comprising minocycline with MgSO₄ and NaOH suitable for intravenous administration is prepared. 100 mg minocycline is added to an aqueous solution of MgSO₄·7H₂O to provide a cation to minocycline molar ratio of 5:1 and a 10 mg/ml minocycline solution. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 4.5-pH 5.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 4.5-pH 5.5 and an osmolality in the range of 150 mOsm/kg-250 mOsm/kg.

Formulation 5

A formulation comprising tigecycline with MgSO₄ and NaOH suitable for intravenous administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of MgSO₄·7H₂O to provide a cation to tigecycline molar ratio of 5:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5-pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5-pH 6.5.

Formulation 6

A formulation comprising tigecycline with MgSO₄ and NaOH suitable for intravenous administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of MgSO₄·7H₂O to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5-pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5-pH 6.5.

Formulation 7

A formulation comprising tigecycline with MgCl₂ and NaOH suitable for intravenous administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of MgCl₂·6H₂O to provide a cation to tigecycline molar ratio of 5:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5-pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5-pH 6.5.

Formulation 8

A formulation comprising tigecycline with MgCl₂ and NaOH suitable for intravenous administration is prepared. 50

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mg tigecycline is added to 10 ml aqueous solution of MgCl₂·6H₂O to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 5.5-pH 6.5. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 5.5-pH 6.5.

Formulation 9

A formulation comprising tigecycline with MgSO₄ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of MgSO₄·7H₂O to provide a cation to tigecycline molar ratio of 5:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0-pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0-pH 7.0.

Formulation 10

A formulation comprising tigecycline with MgSO₄ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of MgSO₄·7H₂O to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0-pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0-pH 7.0.

Formulation 11

A formulation comprising tigecycline with CaCl₂ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of CaCl₂·6H₂O to provide a cation to tigecycline molar ratio of 5:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0-pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0-pH 7.0.

Formulation 12

A formulation comprising tigecycline with CaCl₂ and NaOH suitable for topical administration is prepared. 50 mg tigecycline is added to 10 ml aqueous solution of CaCl₂·6H₂O to provide a cation to tigecycline molar ratio of 12:1. The pH of the solution is adjusted by adding NaOH to a pH in the range of pH 6.0-pH 7.0. The solution is then lyophilized to dryness. Reconstitution of the lyophile in 10 ml water results in a solution having a pH in the range of pH 6.0-pH 7.0.

Example 14

Minocycline Kits

Kit 1

A kit is prepared comprising two vials. The first vial is prepared by dissolving 108 mg minocycline HCl in an acidic solution. The solution is lyophilized to dryness. The second vial contains 10 ml diluent that includes 26.9 mg/ml MgSO₄·7H₂O and 13.6 mg/mL Na(C₂H₃O₂)₂·3H₂O. The lyophile is then reconstituted with the diluent prior to use.

Kit 2

A kit is prepared comprising two vials. The first vial is prepared by dissolving 108 mg minocycline HCl in an acidic solution. The solution is lyophilized to dryness. The second vial contains 10 ml diluent that includes 26.9 mg/ml MgSO₄·7H₂O and enough NaOH to adjust the pH to approximately 5. The lyophile is then reconstituted with the diluent prior to use.

All references cited herein, including but not limited to published and unpublished applications, patents, and litera-

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ture references, are incorporated herein by reference in their entirety and are hereby made a part of this specification. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material. The term “comprising” as used herein is synonymous with “including,” “containing,” or “characterized by,” and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth herein are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of any claims in any application claiming priority to the present application, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

The above description discloses several methods and materials of the present invention. This invention is susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this disclosure or practice of the invention disclosed herein. Consequently, it is not intended that this invention be limited to the specific embodiments disclosed herein, but that it cover all modifications and alternatives coming within the true scope and spirit of the invention.

What is claimed is:

1. A method of treating a bacterial infection in a subject, wherein the method comprises administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration, wherein the composition comprises an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a magnesium cation, wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and wherein the solution does not comprise a pharmaceutically acceptable oil, has a pH greater than 4 and less than 7, and has an osmolality less than about 500 mOsm/kg.

2. The method of claim 1, wherein the solution does not comprise an antioxidant, a pyridine-containing compound, gluconate, an alcohol, glycerol, polyethylene glycol, a pyrrolidone-containing compound, a water-miscible local anesthetic, urea, lactose, or a dehydrating agent.

3. The method of claim 1, wherein solution does not comprise nicotinamide, procaine, or a dehydrating agent selected from the group consisting of ethyl acetate, acetic anhydride, absolute ethanol, and mixtures thereof.

4. The method of claim 1, wherein the solution has a pH of less than 6.

5. The method of claim 1, wherein the solution has a pH of less than 5.

6. The method of claim 1, wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is greater than or equal to 5:1.

7. The method of claim 1, wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is greater than 8:1.

8. The method of claim 1, wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is greater than or equal to 10:1.

9. The method of claim 1, wherein the osmolality of the solution is less than 400 mOsm/kg.

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10. The method of claim 1, wherein the osmolality of the solution is less than 350 mOsm/kg.

11. The method of claim 1, wherein the solution comprises magnesium sulfate.

12. The method of claim 1, wherein the solution comprises magnesium acetate.

13. The method of claim 1, wherein the solution comprises magnesium chloride.

14. The method of claim 1, wherein the solution comprises a buffer.

15. The method of claim 14, wherein the solution comprises acetate.

16. The method of claim 1, wherein the solution comprises a base.

17. The method of claim 16, wherein the base is NaOH.

18. The method of claim 1, wherein the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline.

19. The method of claim 18, wherein the glycylcycline is tigecycline.

20. The method of claim 19, wherein the composition comprises 5 mg/ml tigecycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 5.5 and less than 6.5.

21. The method of claim 19, wherein the composition comprises 5 mg/ml tigecycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 5.5 and less than 6.5.

22. The method of claim 19, wherein the composition comprises 5 mg/ml tigecycline, MgCl_2 , and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 5.5 and less than 6.5.

23. The method of claim 19, wherein the composition comprises 5 mg/ml tigecycline, MgCl_2 , and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 5.5 and less than 6.5.

24. The method of claim 19, wherein the composition comprises 5 mg/ml tigecycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 5:1, and the pH is greater than 6.0 and less than 7.0.

25. The method of claim 19, wherein the composition comprises 5 mg/ml tigecycline, MgSO_4 , and NaOH, wherein the Mg to tigecycline molar ratio is 12:1, and the pH is greater than 6.0 and less than 7.0.

26. The method of claim 1, wherein the 7-dimethylamino-tetracycline is PTK796.

27. The method of claim 1, wherein the 7-dimethylamino-tetracycline is minocycline.

28. The method of claim 27, wherein the concentration of minocycline is at least 5 mg/ml.

29. The method of claim 27, wherein the concentration of minocycline is at least 10 mg/ml.

30. The method of claim 27, wherein the composition comprises 10 mg/ml minocycline, MgCl_2 , and NaOH, wherein the Mg to minocycline molar ratio is 5:1, and the pH is greater than 4.5 and less than 5.5.

31. The method of claim 27, wherein the composition comprises 10 mg/ml minocycline, MgSO_4 , and sodium acetate, wherein the Mg to minocycline molar ratio is 5:1, the pH is greater than 4.5 and less than 5.5, and the osmolality is greater than 275 mOsm/kg and less than 375 mOsm/kg.

32. The method of claim 27, wherein the composition comprises 10 mg/ml minocycline and $\text{Mg}(\text{CH}_3\text{O}_2)_2$, wherein the Mg to minocycline molar ratio is 5:1, and the pH is greater than 4.5 and less than 5.5.

33. The method of claim 27, wherein the composition comprises 10 mg/ml minocycline, MgSO_4 , and NaOH,

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wherein the Mg to minocycline molar ratio is 5:1, the pH is greater than 4.5 and less than 5.5, and the osmolality is greater than 150 mOsm/kg and less than 250 mOsm/kg.

34. A method of treating a bacterial infection in a subject, wherein the method comprises:

reconstituting a water-soluble solid composition in a pharmaceutically acceptable diluent to form a first solution; diluting the reconstituted solution with a pharmaceutically acceptable diluent to form a second solution; and

administering a therapeutically effective amount of the second solution to a subject in need thereof via an intravenous route of administration, wherein the water-soluble solid composition comprises a 7-dimethylamino-tetracycline antibiotic or a salt thereof and a salt comprising a divalent or trivalent metal cation, wherein the molar ratio of divalent or trivalent cation to 7-dimethylamino-tetracycline is greater than 3:1 and wherein the second solution has a pH greater than 4 and less than 7 and an osmolality less than 500 mOsmol/kg.

35. The method of claim 34, wherein the molar ratio of divalent or trivalent metal cation to 7-dimethylamino-tetracycline antibiotic is greater than or equal to 5:1.

36. The method of claim 34, wherein the molar ratio of divalent or trivalent metal cation to 7-dimethylamino-tetracycline antibiotic is greater than 8:1.

37. The method of claim 34, wherein the molar ratio of divalent or trivalent metal cation to 7-dimethylamino-tetracycline antibiotic is greater than or equal to 10:1.

38. The method of claim 34, wherein the water-soluble solid composition is in the form of a lyophile.

39. The method of claim 34, wherein the salt comprising a divalent or trivalent metal cation is magnesium sulfate.

40. The method of claim 34, wherein the salt comprising a divalent or trivalent metal cation is calcium chloride.

41. The method of claim 34, wherein the water-soluble solid composition comprises sodium acetate.

42. The method of claim 34, wherein the water-soluble solid composition comprises NaOH.

43. The method of claim 34, wherein the salt comprising a divalent or trivalent metal cation is selected from magnesium chloride, magnesium bromide, magnesium sulfate, calcium chloride, calcium bromide, zinc chloride, gallium chloride, magnesium malate, magnesium citrate, magnesium acetate, and zinc acetate.

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44. The method of claim 34, wherein the water-soluble solid composition does not comprise an antioxidant, a pyridine-containing compound, nicotinamide, or gluconate.

45. The method of claim 34, wherein the 7-dimethylamino-tetracycline is selected from minocycline, PTK796, and a glycylcycline.

46. The method of claim 45, wherein the glycylcycline is tigecycline.

47. The method of claim 34, wherein the 7-dimethylamino-tetracycline is minocycline.

48. The method of claim 34, wherein the 7-dimethylamino-tetracycline is PTK796.

49. The method of claim 1, wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is from 5:1 to 10:1.

50. The method of claim 49, wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is 5:1.

51. The method of claim 34 wherein the molar ratio of divalent or trivalent metal cation to 7-dimethylamino-tetracycline antibiotic is from 5:1 to 10:1.

52. The method of claim 51, wherein the molar ratio of divalent or trivalent metal cation to 7-dimethylamino-tetracycline antibiotic is 5:1.

53. The method of claim 1, wherein less than 1000 ml of the solution is administered to the subject.

54. The method of claim 1, wherein less than 500 ml of the solution is administered to the subject.

55. The method of claim 1, wherein less than 200 ml of the solution is administered to the subject.

56. The method of claim 1, wherein less than 110 ml of the solution is administered to the subject.

57. The method of claim 34, wherein less than 1000 ml of the second solution is administered to the subject.

58. The method of claim 34, wherein less than 500 ml of the second solution is administered to the subject.

59. The method of claim 34, wherein less than 200 ml of the second solution is administered to the subject.

60. The method of claim 34, wherein less than 110 ml of the second solution is administered to the subject.

* * * * *

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AO279,APPEAL,PROTO,TERMED,VALDEZ

United States District Court
Northern District of Illinois - CM/ECF NextGen 1.8 (rev. 1.8.2) (Chicago)
CIVIL DOCKET FOR CASE #: 1:21-cv-02636

Melinta Therapeutics, LLC et al v. Nexus Pharmaceuticals, Inc.
Assigned to: Honorable John F. Kness
related Case: [1:21-cv-05995](#)
Case in other court: 25-01281
Cause: 35:271 Patent Infringement

Date Filed: 05/14/2021
Date Terminated: 11/15/2024
Jury Demand: None
Nature of Suit: 835 Patent - Abbreviated
New Drug Application(ANDA)
Jurisdiction: Federal Question

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Date Filed	#	Docket Text
05/14/2021	<u>1</u>	COMPLAINT filed by Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc., Melinta Subsidiary Corp.; Filing fee \$ 402, receipt number 0752-18250241. (Attachments: # <u>1</u> Exhibit A, # <u>2</u> Exhibit B, # <u>3</u> Exhibit C, # <u>4</u> Exhibit D)(Hood, Gary) (Entered: 05/14/2021)
05/14/2021	<u>2</u>	CIVIL Cover Sheet (Hood, Gary) (Entered: 05/14/2021)
05/14/2021	<u>3</u>	ATTORNEY Appearance for Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. by Gary Edward Hood (Hood, Gary) (Entered: 05/14/2021)
05/14/2021	<u>4</u>	NOTIFICATION of Affiliates pursuant to Local Rule 3.2 by All Plaintiffs (Hood, Gary) (Entered: 05/14/2021)
05/14/2021	<u>5</u>	ATTORNEY Appearance for Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. by Mark Thomas Deming (Deming, Mark) (Entered: 05/14/2021)
05/14/2021	<u>6</u>	Notice of Claims Involving Patents under Local Rule 3.4 by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Hood, Gary) (Entered: 05/14/2021)
05/17/2021	<u>7</u>	MAILED patent report to Patent Trademark Office, Alexandria VA (exr,) (Entered: 05/17/2021)
05/17/2021		CASE ASSIGNED to the Honorable John F. Kness. Designated as Magistrate Judge the Honorable Maria Valdez. Case assignment: Random assignment. (mp,) (Entered: 05/17/2021)
06/01/2021	<u>8</u>	ATTORNEY Appearance for Defendant Nexus Pharmaceuticals, Inc. by Joel M Wallace (Wallace, Joel) (Entered: 06/01/2021)
06/01/2021	<u>9</u>	SEALED DOCUMENT by Defendant Nexus Pharmaceuticals, Inc. <i>Answer, Affirmative Defenses, and Counterclaims</i> (Wallace, Joel) (Entered: 06/01/2021)
06/01/2021	<u>10</u>	<i>REDACTED</i> ANSWER to Complaint , <i>Affirmative Defenses, and</i> COUNTERCLAIM filed by Nexus Pharmaceuticals, Inc. against All Plaintiffs . by Nexus Pharmaceuticals, Inc.(Wallace, Joel) (Entered: 06/01/2021)
06/01/2021	<u>11</u>	MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. to seal document sealed document <u>9</u> (Wallace, Joel) (Entered: 06/01/2021)
06/07/2021	<u>12</u>	MINUTE entry before the Honorable John F. Kness: Defendant's Motion to for leave to file under seal document <u>11</u> is granted. Mailed notice (ef,) (Entered: 06/07/2021)

06/10/2021	<u>13</u>	ATTORNEY Appearance for Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. by Brian Neil Anderson (Anderson, Brian) (Entered: 06/10/2021)
06/11/2021	<u>14</u>	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for extension of time <i>for Exchange of Initial Disclosures under Local Patent Rule 2.1</i> (Hood, Gary) (Entered: 06/11/2021)
06/15/2021	<u>15</u>	ATTORNEY Appearance for Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. by Imron T Aly (Aly, Imron) (Entered: 06/15/2021)
06/15/2021	<u>16</u>	PROPOSED BRIEFING SCHEDULE FOR PLAINTIFFS' OPPOSED MOTION FOR 45-DAY EXTENSION TO LOCAL PATENT RULE 2.1 INITIAL DISCLOSURES STATEMENT by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Hood, Gary) (Entered: 06/15/2021)
06/16/2021	<u>17</u>	MINUTE entry before the Honorable John F. Kness: By agreement of the parties, the Court sets the following briefing schedule on Plaintiffs' Opposed Motion For 45-Day Extension To Local Patent Rule 2.1 Initial Disclosures <u>14</u> : Defendant must respond on or before 6/21/2021 and Plaintiffs must reply on or before 6/28/2021. Within one week of filing, each side must provide two paper courtesy copies of their respective briefs to chambers via U.S. Mail or reliable commercial delivery service. Mailed notice (ef,) (Entered: 06/16/2021)
06/21/2021	<u>18</u>	RESPONSE by Nexus Pharmaceuticals, Inc.in Opposition to MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for extension of time <i>for Exchange of Initial Disclosures under Local Patent Rule 2.1</i> <u>14</u> (Wallace, Joel) (Entered: 06/21/2021)
06/22/2021	<u>19</u>	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for leave to file <i>UNDER SEAL</i> (Anderson, Brian) (Entered: 06/22/2021)
06/22/2021	<u>20</u>	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>PLAINTIFFS' ANSWER TO THE COUNTERCLAIMS OF DEFENDANT NEXUS PHARMACEUTICALS, INC.</i> (Anderson, Brian) (Entered: 06/22/2021)
06/22/2021	<u>21</u>	<i>REDACTED</i> ANSWER to counterclaim <i>OF DEFENDANT NEXUS PHARMACEUTICALS, INC.</i> by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc.(Anderson, Brian) (Entered: 06/22/2021)
06/25/2021	<u>22</u>	MINUTE entry before the Honorable John F. Kness: Plaintiffs' Motion for leave to file document under seal <u>19</u> is granted. Mailed notice (ef,) (Entered: 06/25/2021)
06/28/2021	<u>23</u>	REPLY by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. to response in opposition to motion, <u>18</u> <i>for 45-Day Extension to Local Patent Rule 2.1 Initial Disclosures</i> (Hood, Gary) (Entered: 06/28/2021)
07/09/2021	<u>24</u>	MOTION for Leave to Appear Pro Hac Vice Filing fee \$ 150, receipt number 0752-18440661. (Chou, Monica) (Entered: 07/09/2021)
07/13/2021	<u>25</u>	MINUTE entry before the Honorable John F. Kness: Motion by counsel for leave to appear pro hac vice <u>24</u> is granted. Mailed notice (ef,) (Entered: 07/13/2021)
08/02/2021	<u>26</u>	MOTION for Leave to Appear Pro Hac Vice Filing fee \$ 150, receipt number 0752-18521468. (Dombrowski, Damien) (Entered: 08/02/2021)

08/04/2021	27	MINUTE entry before the Honorable John F. Kness: Motion by counsel for leave to appear pro hac vice 26 is granted. Mailed notice (ef,) (Entered: 08/04/2021)
08/05/2021	28	MINUTE entry before the Honorable John F. Kness: Telephonic motion and status hearing set for 8/24/2021 at 09:30 AM. The parties are to use the following call-in number: 888-684-8852, conference code 3796759. The public and media representatives may have access to the hearing via the same number. Audio recording of the hearing is not permitted; violations of this prohibition may result in sanctions. Participants are directed to keep their device muted when they are not speaking. Mailed notice (ef,) (Entered: 08/05/2021)
08/09/2021		SUMMONS Issued as to Defendant Nexus Pharmaceuticals, Inc. (jmk,) (Entered: 08/09/2021)
08/20/2021	29	STATUS Report by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Attachments: # 1 Exhibit 1)(Anderson, Brian) (Entered: 08/20/2021)
08/24/2021	30	MOTION for Leave to Appear Pro Hac Vice Filing fee \$ 150, receipt number 0752-18594306. (Wong, Ha Kung) (Entered: 08/24/2021)
08/24/2021	31	MINUTE entry before the Honorable John F. Kness: Telephonic status hearing held on 8/24/2021. For the reasons stated on the record, Plaintiffs' motion for 45-day extension to Local Patent Rule 2.1 initial disclosures 14 is denied. The parties are directed to meet and confer concerning a proposed scheduling order to govern the remainder of this litigation. On or before 9/3/2021, the parties must file a joint status report and submit a Word version of their proposed scheduling order under Rule 16(b) (or competing proposals, if the parties cannot agree) to the Court's proposed order mailbox, Proposed_Order_Kness@ilnd.uscourts.gov. Motion by counsel for leave to appear pro hac vice 30 is granted. A continued status hearing is set for 9/7/2021 at 10:15 AM; NOTE TIME CHANGE. The parties shall use the same call-in information 28 . Mailed notice (ef,) (Entered: 08/24/2021)
08/25/2021	32	ENTERED in Error (gw,) Modified on 8/25/2021 (gw,). (Entered: 08/25/2021)
08/25/2021	33	NOTICE of Correction 32 (gw,) (Entered: 08/25/2021)
09/03/2021	34	STATUS Report by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Attachments: # 1 Exhibit 1)(Anderson, Brian) (Entered: 09/03/2021)
09/07/2021	35	MINUTE entry before the Honorable John F. Kness: Telephone status hearing held. For the reasons provided by the parties, the Court adopts the parties' proposed schedule. Enter separate Scheduling Order. The case will be referred to the magistrate judge for discovery supervision. The magistrate judge is given full authority to amend the scheduling order as needed. Mailed notice (ags) (Entered: 09/07/2021)
09/07/2021	36	SCHEDULING ORDER signed by the Honorable John F. Kness on 9/7/2021. Mailed notice (ags) (Entered: 09/07/2021)
09/07/2021	37	Pursuant to Local Rule 72.1, this case is hereby referred to the calendar of Honorable Maria Valdez for the purpose of holding proceedings related to: discovery supervision. (ags) Mailed notice. (Entered: 09/07/2021)
09/08/2021	38	MINUTE entry before the Honorable Maria Valdez: This matter has been referred to Judge Valdez for discovery supervision. The parties are to file a joint status report no later than 12/10/21 detailing their discovery progress. Mailed notice (lp,) (Entered: 09/08/2021)

11/05/2021	39	MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. to dismiss <i>Count I for Lack of Subject Matter Jurisdiction, Failure to State a Claim, and Primary Jurisdiction</i> (Wallace, Joel) (Entered: 11/05/2021)
11/05/2021	40	MEMORANDUM by Nexus Pharmaceuticals, Inc. in support of motion to dismiss 39 <i>Count I for Lack of Subject Matter Jurisdiction, Failure to State a Claim, and Primary Jurisdiction</i> (Attachments: # 1 Exhibit 1)(Wallace, Joel) (Entered: 11/05/2021)
11/09/2021	41	MINUTE entry before the Honorable John F. Kness: The Court sets the following briefing schedule on motion to dismiss 39 : any responses must be filed on or before 12/7/2021 and any must replies must be filed on or before 12/21/2021. Within one week of filing, each side must provide two paper courtesy copies of their respective briefs to chambers via U.S. Mail or reliable commercial delivery service. Mailed notice (ef,) (Entered: 11/09/2021)
11/23/2021	42	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. to consolidate cases (Attachments: # 1 Exhibit 1, # 2 Exhibit 2) (Anderson, Brian) (Entered: 11/23/2021)
12/02/2021	43	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for extension of time to file response/reply as to motion to dismiss 39 (Attachments: # 1 Exhibit 1)(Anderson, Brian) (Entered: 12/02/2021)
12/03/2021	44	ATTORNEY Appearance for Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. by Helen H Ji (Ji, Helen) (Entered: 12/03/2021)
12/07/2021	45	ORDER: Before the Court is Plaintiffs' unopposed motion to consolidate 42 . For the reasons stated by Plaintiffs, the motion is granted. Cases 21-cv-2636 and 21-cv-5995 are consolidated for all pretrial purposes and for trial, but the cases are not merged. Rather, separate judgments will be required in each case. See generally 9 Charles Alan Wright et al., Federal Practice and Procedure § 2382 (explaining various types of consolidation). All pleadings are to be filed in the lead case number, 21-cv-2636. All pending parties and counsel in the associated case, 21-cv-5995, are to be linked to the lead case number, 21-cv-2636. Joint motion for extension of time to file response/reply 43 is granted. The briefing schedule on motion to dismiss 39 is extended as follows: any responses must be filed on or before 12/21/2021 and any must replies must be filed on or before 1/18/2022. Within one week of filing, each side must provide two paper courtesy copies of their respective briefs to chambers via U.S. Mail or reliable commercial delivery service. Status hearing set for 2/14/2022 at 9:50 AM. The parties shall use the same call-in information 28 . Signed by the Honorable John F. Kness on 12/7/2021: Mailed notice. (rc,) (Entered: 12/08/2021)
12/10/2021	46	STATUS Report <i>JOINT STATUS REPORT REGARDING DISCOVERY</i> by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Attachments: # 1 Exhibit 1 - Minute Entry (38), # 2 Exhibit 2 - Scheduling Order (36), # 3 Exhibit 3 - FedEx Subpoena)(Anderson, Brian) (Entered: 12/10/2021)
12/13/2021	47	MINUTE entry before the Honorable Maria Valdez: The parties are to file a further joint status report by 2/18/22. Mailed notice (lp,) (Entered: 12/13/2021)
12/17/2021	48	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for leave to file excess pages <i>PLAINTIFFS' UNOPPOSED MOTION TO EXCEED PAGE LIMIT</i> (Anderson, Brian) (Entered: 12/17/2021)
12/21/2021	49	RESPONSE by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc.in Opposition to MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. to dismiss <i>Count I for Lack</i>

		<i>of Subject Matter Jurisdiction, Failure to State a Claim, and Primary Jurisdiction</i> 39 (Anderson, Brian) (Entered: 12/21/2021)
12/22/2021	50	MINUTE entry before the Honorable John F. Kness: Plaintiffs' Unopposed Motion for leave to file excess pages 48 is granted. Mailed notice (ef,) (Entered: 12/22/2021)
01/13/2022	51	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc.To Establish Procedure For Potential Preliminary Injunction Proceedings (Attachments: # 1 Exhibit 1, # 2 Exhibit 2)(Anderson, Brian) (Entered: 01/13/2022)
01/13/2022	52	Proposed Scheduling Order For Plaintiffs Opposed Motion To Establish Procedure For Potential Preliminary Injunction Proceedings STATEMENT by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Anderson, Brian) (Entered: 01/13/2022)
01/14/2022	53	MINUTE entry before the Honorable John F. Kness: By agreement of the parties, the Court sets the following briefing schedule on Plaintiffs' motion to establish a procedure for potential preliminary injunction 51 : Defendant's response must be filed on or before 2/15/2022 and Plaintiffs replies must be filed on or before 3/1/2022. Within one week of filing, each side must provide two paper courtesy copies of their respective briefs to chambers via U.S. Mail or reliable commercial delivery service..Mailed notice (ef,) (Entered: 01/14/2022)
01/18/2022	54	REPLY by Nexus Pharmaceuticals, Inc. to memorandum in support of motion 40 , response in opposition to motion, 49 , MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. to dismiss <i>Count I for Lack of Subject Matter Jurisdiction, Failure to State a Claim, and Primary Jurisdiction</i> 39 (Ji, Helen) (Entered: 01/18/2022)
01/21/2022	55	RESPONSE by Nexus Pharmaceuticals, Inc.in Opposition to MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc.To Establish Procedure For Potential Preliminary Injunction Proceedings 51 (Ji, Helen) (Entered: 01/21/2022)
02/10/2022	56	MINUTE entry before the Honorable John F. Kness: To give the parties time to complete briefing on Plaintiffs' motion 51 to establish procedure for potential preliminary injunction proceedings, status hearing set for 02/14/2022 is stricken and reset to 3/17/2022 at 09:30 AM. Parties shall use the same call-in information 28 . Mailed notice (ef,) (Entered: 02/10/2022)
02/18/2022	57	STATUS Report <i>Joint Status Report Regarding Discovery</i> by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Anderson, Brian) (Entered: 02/18/2022)
02/22/2022	58	MINUTE entry before the Honorable Maria Valdez: The parties' joint request to extend the preliminary close of fact discovery to 4/18/22 is granted. A further status report is to be filed by 4/1/22. The parties are strongly encouraged to continue meeting and conferring in order to resolve any discovery disputes without the need for judicial intervention. Mailed notice (lp,) (Entered: 02/22/2022)
03/01/2022	59	MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. to quash <i>Plaintiffs' Subpoena on Schiff Hardin LLP</i> , MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. for protective order <i>for Schiff Hardin LLP</i> (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H, # 9 Exhibit I, # 10 Exhibit J)(Wallace, Joel) (Entered: 03/01/2022)

03/01/2022	60	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for leave to file <i>Under Seal</i> (Anderson, Brian) (Entered: 03/01/2022)
03/01/2022	61	SEALED REPLY by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. to MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. To Establish Procedure For Potential Preliminary Injunction Proceedings 51 (Attachments: # 1 Exhibit A, # 2 Exhibit B) (Anderson, Brian) (Entered: 03/01/2022)
03/01/2022	62	REPLY by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. to MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. To Establish Procedure For Potential Preliminary Injunction Proceedings 51 , response in opposition to motion, 55 <i>REDACTED</i> (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Anderson, Brian) (Entered: 03/01/2022)
03/02/2022	63	MINUTE entry before the Honorable Maria Valdez: Plaintiff's response to Defendant's and Non-Party Schiff Hardin LLP's Motion to Quash 59 is due by 3/16/22, and Defendant's reply is due 3/23/22. Mailed notice (lp,) (Entered: 03/02/2022)
03/03/2022	64	MINUTE entry before the Honorable John F. Kness: Plaintiffs' Motion for leave to file under seal 60 is granted. The status hearing set for 3/17/2022 at 9:30 AM is reset for 3/17/2022 at 09:15 AM. TIME CHANGE ONLY. Plaintiffs' motion 51 to establish procedure for potential preliminary injunction proceedings will be discussed at the 3/17 hearing. Mailed notice (ef,) (Entered: 03/03/2022)
03/16/2022	65	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for leave to file <i>Under Seal</i> (Anderson, Brian) (Entered: 03/16/2022)
03/16/2022	66	SEALED RESPONSE by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. to MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. to quash <i>Plaintiffs' Subpoena on Schiff Hardin LLP</i> MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. for protective order <i>for Schiff Hardin LLP</i> 59 (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4)(Anderson, Brian) (Entered: 03/16/2022)
03/16/2022	67	RESPONSE by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. in Opposition to MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. to quash <i>Plaintiffs' Subpoena on Schiff Hardin LLP</i> MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. for protective order <i>for Schiff Hardin LLP</i> 59 <i>REDACTED</i> (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4) (Anderson, Brian) (Entered: 03/16/2022)
03/17/2022	68	MINUTE entry before the Honorable Maria Valdez: Plaintiffs' Unopposed Motion for Leave to File Under Seal 65 is granted. Plaintiffs are given leave to file their brief in opposition to the motion to quash 59 under seal. Mailed notice (lp,) (Entered: 03/17/2022)
03/17/2022	69	MINUTE entry before the Honorable John F. Kness: Telephonic status hearing held on 3/17/2022. For the reasons stated on the record, Plaintiffs' motion to establish a procedure for potential preliminary injunction 51 is denied. A continued status hearing is set for 4/27/2022 at 10:10 AM; parties shall use the same call-in information 28 . Mailed notice (ef,) (Entered: 03/18/2022)

03/21/2022	70	STATUS Report <i>Joint Status Report Regarding Claim Construction</i> by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Anderson, Brian) (Entered: 03/21/2022)
03/23/2022	71	REPLY by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. to motion to quash,, motion for protective order,, 59 , response in opposition to motion,, 67 (Wallace, Joel) (Entered: 03/23/2022)
03/30/2022	72	MINUTE entry before the Honorable Maria Valdez: Defendant's and Non-Party Schiff Hardin LLP's Motion to Quash and Objections to Plaintiffs' Rule 45 Subpoena to Defendant Nexus's Litigation Counsel 59 is granted. The parties' 4/1/22 status report should include a joint proposed expert discovery schedule. Mailed notice (lp,) (Entered: 03/30/2022)
03/30/2022	73	ORDER. Signed by the Honorable Maria Valdez on 3/30/2022: Mailed notice (lp,) (Entered: 03/30/2022)
04/01/2022	74	NOTICE by Joel M Wallace of Change of Address (Wallace, Joel) (Entered: 04/01/2022)
04/01/2022	75	STATUS Report <i>Joint Status Report Regarding Discovery</i> by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Anderson, Brian) (Entered: 04/01/2022)
04/04/2022	76	MINUTE entry before the Honorable Maria Valdez: The expert discovery schedule is entered as follows: initial expert witness disclosures on issues for which either party bears the burden of proof are due by 6/15/22; rebuttal expert witness disclosures on issues for which the opposing party bears the burden of proof are due 7/29/22; and all experts are to be deposed no later than 8/31/22. The parties do not mutually agree to reply expert reports, so they are not included in the schedule. Cf. Sloan Valve Co. v. Zurn Indus. Inc., No. 10 C 204, 2013 WL 3147349, at *1 (N.D. Ill. June 19, 2013). Mailed notice (lp,) (Entered: 04/04/2022)
04/06/2022	77	ENTERED IN ERROR. (Labella, Nancy) Modified on 4/6/2022 (jn,). (Entered: 04/06/2022)
04/06/2022	78	CORRECTED TRANSCRIPT OF PROCEEDINGS held on 3/17/22 before the Honorable John F. Kness. Order Number: 42848. Court Reporter Contact Information: Nancy LaBella, 312-435-6890, nlabella.ilnd@gmail.com. <P>IMPORTANT: The transcript may be viewed at the court's public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through the Court Reporter/Transcriber or PACER. For further information on the redaction process, see the Court's web site at www.ilnd.uscourts.gov under Quick Links select Policy Regarding the Availability of Transcripts of Court Proceedings.</P> Redaction Request due 4/27/2022. Redacted Transcript Deadline set for 5/9/2022. Release of Transcript Restriction set for 7/5/2022. (Labella, Nancy) (Entered: 04/06/2022)
04/06/2022	79	NOTICE of Correction regarding document 77 . (jn,) (Entered: 04/06/2022)
04/07/2022	80	NOTICE by Imron T Aly of Change of Address (Aly, Imron) (Entered: 04/07/2022)
04/08/2022	81	MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. for protective order <i>from Disclosure to Proposed Expert</i> (Attachments: # 1 Exhibit A)(Wallace, Joel) (Entered: 04/08/2022)
04/11/2022	82	MINUTE entry before the Honorable Maria Valdez: Plaintiffs' response to Defendant's Motion for a Protective Order 81 is due by 4/25/22, and Defendant's reply is due 5/2/22. Mailed notice (lp,) (Entered: 04/11/2022)

04/18/2022	83	MOTION by Attorney Gary E. Hood to withdraw as attorney for Melinta Subsidiary Corp., Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Melinta Therapeutics, LLC. No party information provided (Hood, Gary) (Entered: 04/18/2022)
04/18/2022	84	MINUTE entry before the Honorable John F. Kness: Motion by counsel to withdraw as attorney 83 is granted. Attorney Gary Edward Hood is withdrawn as counsel of record. Mailed notice (ef,) (Entered: 04/18/2022)
04/18/2022	85	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for extension of time to complete discovery <i>Joint Motion to Extend LPR 1.3 Preliminary Close of Fact Discovery</i> (Anderson, Brian) (Entered: 04/18/2022)
04/19/2022	86	MINUTE entry before the Honorable Maria Valdez: The parties' Joint Motion to Extend LPR 1.3 Preliminary Close of Fact Discovery 85 is granted. The preliminary close of fact discovery is extended to 5/10/22 for the sole purpose of completing the two previously noticed depositions listed in the motion. Mailed notice (lp,) (Entered: 04/19/2022)
04/25/2022	87	ATTORNEY Appearance for Defendant Nexus Pharmaceuticals, Inc. by Kevin Michael Nelson <i>ArentFox Schiff, LLP</i> (Nelson, Kevin) (Entered: 04/25/2022)
04/25/2022	88	MEMORANDUM by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. in Opposition to motion for protective order 81 (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4)(Anderson, Brian) (Entered: 04/25/2022)
04/26/2022	89	MINUTE entry before the Honorable John F. Kness: To allow the parties time to complete fact discovery, and in view of the pending but not yet fully briefed motion 81 before Magistrate Judge Valdez for a protective order, the status hearing set before Judge Kness for 04/27/2022 is stricken and reset to 5/31/2022 at 10:10 AM. Parties shall use the same call-in information 28 . Mailed notice (ef,) (Entered: 04/26/2022)
05/02/2022	90	REPLY by Nexus Pharmaceuticals, Inc. to memorandum in opposition to motion, 88 , MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. for protective order <i>from Disclosure to Proposed Expert</i> 81 (Ji, Helen) (Entered: 05/02/2022)
05/04/2022	91	MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. to compel <i>the production of documents</i> (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5)(Wallace, Joel) (Entered: 05/04/2022)
05/05/2022	92	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for leave to file <i>Sur-Reply Brief Or In The Alternative Deem Defendant's New Arguments Waived</i> (Attachments: # 1 Exhibit 1 (proposed sur-reply)) (Anderson, Brian) (Entered: 05/05/2022)
05/06/2022	93	MINUTE entry before the Honorable Maria Valdez: Plaintiff's response to Defendant's Motion to Compel Document Production from Plaintiffs 91 is due by 5/20/22, and Defendant's reply is due 5/27/22. Mailed notice (lp,) (Entered: 05/06/2022)
05/06/2022	94	MINUTE entry before the Honorable Maria Valdez: Plaintiffs' Opposed Motion for Leave to File Sur-Reply Brief or in the Alternative to Deem Defendant's New Arguments Waived 92 is denied. The Court is well aware that new arguments may not be raised in a reply brief and is capable of disregarding them without the benefit of a sur-reply. Mailed notice (lp,) (Entered: 05/06/2022)
05/20/2022	95	MEMORANDUM by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. in Opposition to motion to compel, 91 (Attachments: # 1 Exhibit 1,

		# 2 Exhibit 2)(Anderson, Brian) (Entered: 05/20/2022)
05/27/2022	96	MINUTE entry before the Honorable Maria Valdez: Defendant's Motion for a Protective Order to Prevent Disclosure of Highly Confidential and Confidential Information to Plaintiffs' Proposed Expert 81 is denied. The expert discovery schedule is extended as follows: initial expert witness disclosures on issues for which either party bears the burden of proof are due by 8/31/22; rebuttal expert witness disclosures on issues for which the opposing party bears the burden of proof are due 10/14/22; and all experts are to be deposed no later than 11/16/22. There will be no further extensions absent extraordinary circumstances. Mailed notice (lp,) (Entered: 05/27/2022)
05/27/2022	97	ORDER. Signed by the Honorable Maria Valdez on 5/27/2022:Mailed notice(lp,) (Entered: 05/27/2022)
05/27/2022	98	MINUTE entry before the Honorable John F. Kness: In view of the pending motion 91 before Magistrate Judge Valdez, status hearing set for 05/31/2022 is stricken and reset to 7/19/2022 at 09:40 AM. Defendant's motion 39 to dismiss Count I remains under advisement. Members of the public and media may listen to these proceedings by dialing 1-888-684-8852 and using access code 3796759. Persons granted remote access to proceedings are reminded of the general prohibition against photographing, recording, and rebroadcasting of court proceedings. Violation of these prohibitions may result in sanctions, including removal of court issued media credentials, restricted entry to future hearings, denial of entry to future hearings, or any other sanctions deemed necessary by the Court.Mailed notice (ef,) (Entered: 05/27/2022)
05/27/2022	99	REPLY by Nexus Pharmaceuticals, Inc. to memorandum in opposition to motion 95 (Attachments: # 1 Exhibit 6)(Wallace, Joel) (Entered: 05/27/2022)
06/06/2022	100	STATUS Report <i>Regarding Protective Order</i> by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Attachments: # 1 Exhibit 1 (Protective Order))(Anderson, Brian) (Entered: 06/06/2022)
06/07/2022	101	MINUTE entry before the Honorable Maria Valdez: As directed in footnote 2 of this Court's 5/27/22 order, the parties are reminded to review the standing order regarding the submission of orders for electronic entry and submit their protective order accordingly. Mailed notice (lp,) (Entered: 06/07/2022)
06/07/2022	102	PROTECTIVE Order. Signed by the Honorable Maria Valdez on 6/7/2022: Mailed notice (lp,) (Entered: 06/07/2022)
07/18/2022	103	MINUTE entry before the Honorable John F. Kness: In view of the motion 9 to compel, which is pending before Magistrate Judge Valdez, as well as the partial motion 39 to dismiss that remains pending before Judge Kness, the status hearing set for 07/19/2022 is stricken and reset to 8/9/2022 at 09:50 AM. The parties are to use the following call-in number: 888-684-8852, conference code 3796759. The public and media representatives may have access to the hearing via the same number. Audio recording of the hearing is not permitted; violations of this prohibition may result in sanctions. Participants are directed to keep their device muted when they are not speaking. Mailed notice (ef,) (Entered: 07/18/2022)
07/21/2022	104	MINUTE entry before the Honorable Maria Valdez: Defendant's Motion to Compel Document Production from Plaintiffs 91 is denied. Status report on expert discovery progress and the prospects of settlement is due no later than 9/23/22. Mailed notice (lp,) (Entered: 07/21/2022)
07/21/2022	105	ORDER. Signed by the Honorable Maria Valdez on 7/21/2022: Mailed notice (lp,) (Entered: 07/21/2022)

07/26/2022	<u>106</u>	MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. for leave to file <i>Supplemental Exhibits to Its Motion to Dismiss (DI 39)</i> (Attachments: # <u>1</u> Exhibit A, # <u>2</u> Exhibit B)(Wallace, Joel) (Entered: 07/26/2022)
07/28/2022	<u>107</u>	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for leave to file excess pages <i>Joint Motion to Exceed Page Limits</i> (Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>108</u>	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for leave to file <i>Under Seal</i> (Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>109</u>	SEALED MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Plaintiffs' Motion For Entry Of A Temporary Restraining Order</i> (Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>110</u>	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Declaration of Monica Chou, Esq. In Support of Plaintiff's Motion For A Temporary Restraining Order</i> (Attachments: # <u>1</u> Exhibit A, # <u>2</u> Exhibit B, # <u>3</u> Exhibit C, # <u>4</u> Exhibit D, # <u>5</u> Exhibit E, # <u>6</u> Exhibit F, # <u>7</u> Exhibit G, # <u>8</u> Exhibit H, # <u>9</u> Exhibit I, # <u>10</u> Exhibit J)(Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>111</u>	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Declaration of Tina deVries, Ph.D., In Support Of Plaintiffs' Motion For Preliminary Injunction</i> (Attachments: # <u>1</u> Exhibit A, # <u>2</u> Exhibit B) (Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>112</u>	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Declaration of John Harlow In Support Of Plaintiffs Motion For A Temporary Restraining Order And Preliminary Injunction</i> (Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>113</u>	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Declaration of Michael E. Tate In Support Of Plaintiffs' Motion For A Temporary Restraining Order</i> (Attachments: # <u>1</u> Exhibit A) (Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>114</u>	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Joint Status Report Regarding TRO Proceedings</i> (Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>115</u>	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for temporary restraining order <i>REDACTED</i> (Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>116</u>	DECLARATION of Monica Chou, Esq. regarding motion for temporary restraining order <u>115</u> , Sealed motion <u>109</u> <i>REDACTED</i> (Attachments: # <u>1</u> Exhibit A, # <u>2</u> Exhibit B, # <u>3</u> Exhibit C, # <u>4</u> Exhibit D, # <u>5</u> Exhibit E, # <u>6</u> Exhibit F, # <u>7</u> Exhibit G, # <u>8</u> Exhibit H (REDACTED), # <u>9</u> Exhibit I (REDACTED), # <u>10</u> Exhibit J (REDACTED))(Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>117</u>	DECLARATION of Tina deVries, Ph.D. regarding motion for temporary restraining order <u>115</u> , Sealed motion <u>109</u> <i>REDACTED</i> (Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>118</u>	DECLARATION of John Harlow regarding motion for temporary restraining order <u>115</u> , Sealed motion <u>109</u> <i>REDACTED</i> (Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	<u>119</u>	DECLARATION of Michael E. Tate regarding motion for temporary restraining order <u>115</u> , Sealed motion <u>109</u> <i>REDACTED</i> (Attachments: # <u>1</u> Exhibit A)(Anderson, Brian)

		(Entered: 07/28/2022)
07/28/2022	120	DECLARATION of Tina deVries, Ph.D. regarding motion for temporary restraining order 115 , Sealed motion 109 REDACTED (WITH EXHIBITS) (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Anderson, Brian) (Entered: 07/28/2022)
07/28/2022	121	STATUS Report REDACTED Joint Status Report Regarding TRO Proceedings by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Anderson, Brian) (Entered: 07/28/2022)
07/29/2022	122	MINUTE entry before the Honorable John F. Kness: The pending motions for leave to file 106 107 108 are granted. The Court sets the following briefing schedule on Plaintiffs' pending motions 109 115 : Responses must respond on or before 8/1/2022 and replies must reply on or before 8/2/2022. Motion Hearing set for 8/4/2022 at 09:00 AM. The parties are to use the following call-in number: 888-684-8852, conference code 3796759. The public and media representatives may have access to the hearing via the same number. Audio recording of the hearing is not permitted; violations of this prohibition may result in sanctions. Participants are directed to keep their device muted when they are not speaking. Mailed notice (ef,) (Entered: 07/29/2022)
07/29/2022	123	MOTION for Leave to Appear Pro Hac Vice Filing fee \$ 150, receipt number BILNDC-19696301. (Anderson, Brian) (Entered: 07/29/2022)
08/01/2022	124	MINUTE entry before the Honorable John F. Kness: Motion by counsel for leave to appear pro hac vice 123 is granted. Mailed notice (ef,) (Entered: 08/01/2022)
08/01/2022	125	MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. to seal document <i>Opposition to Plaintiffs' Motion for TRO</i> (Wallace, Joel) (Entered: 08/01/2022)
08/01/2022	126	SEALED RESPONSE by Nexus Pharmaceuticals, Inc. to MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for temporary restraining order REDACTED 115 , SEALED MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Plaintiffs' Motion For Entry Of A Temporary Restraining Order</i> 109 (Wallace, Joel) (Entered: 08/01/2022)
08/01/2022	127	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Declaration of Joel M. Wallace In Support of Nexus's Opposition to Plaintiffs' Motion for a TRO</i> (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10, # 11 Exhibit 11, # 12 Exhibit 12, # 13 Exhibit 13, # 14 Exhibit 14, # 15 Exhibit 15, # 16 Exhibit 16, # 17 Exhibit 17, # 18 Exhibit 18, # 19 Exhibit 19) (Wallace, Joel) (Entered: 08/01/2022)
08/01/2022	128	RESPONSE by Nexus Pharmaceuticals, Inc.in Opposition to MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for temporary restraining order REDACTED 115 , SEALED MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Plaintiffs' Motion For Entry Of A Temporary Restraining Order</i> 109 REDACTED VERSION (Wallace, Joel) (Entered: 08/01/2022)
08/01/2022	129	DECLARATION of Joel M. Wallace regarding response in opposition to motion, 128 <i>PUBLIC VERSIONS</i> (Attachments: # 1 Exhibit 1, # 2 Exhibit 2 (Redacted), # 3 Exhibit 3 (Redacted), # 4 Exhibit 4 (Redacted), # 5 Exhibit 5 (Redacted), # 6 Exhibit 6 (Redacted), # 7 Exhibit 7 (Redacted), # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10 (Redacted), # 11 Exhibit 11 (Redacted), # 12 Exhibit 12 (Redacted), # 13 Exhibit 13, # 14 Exhibit 14, # 15

		Exhibit 15 (Redacted), # 16 Exhibit 16, # 17 Exhibit 17, # 18 Exhibit 18, # 19 Exhibit 19) (Wallace, Joel) (Entered: 08/01/2022)
08/01/2022	130	DECLARATION of Tina deVries, Ph.D. regarding motion for temporary restraining order 115 , Sealed motion 109 REDACTED (CORRECTED) (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Anderson, Brian) (Entered: 08/01/2022)
08/02/2022	131	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for leave to file <i>Under Seal</i> (Anderson, Brian) (Entered: 08/02/2022)
08/02/2022	132	SEALED REPLY by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. to MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for temporary restraining order REDACTED 115 , SEALED MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Plaintiffs' Motion For Entry Of A Temporary Restraining Order</i> 109 (Anderson, Brian) (Entered: 08/02/2022)
08/02/2022	133	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Declaration of Bruce Friedman, M.D. In Support of Plaintiffs' Motion for Preliminary Injunction</i> (Attachments: # 1 Exhibit A, # 2 Exhibit B) (Anderson, Brian) (Entered: 08/02/2022)
08/02/2022	134	REPLY by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. to motion for temporary restraining order 115 , Sealed motion 109 REDACTED (Anderson, Brian) (Entered: 08/02/2022)
08/02/2022	135	DECLARATION of Bruce Friedman, M.D. regarding reply, 132 <i>In Support of Plaintiffs' Motion for Preliminary Injunction</i> (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Anderson, Brian) (Entered: 08/02/2022)
08/02/2022	136	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Second Declaration of M. Chou, Esq. In Support of Plaintiffs' Motion for Entry Of A Temporary Restraining Order</i> (Attachments: # 1 Exhibit K, # 2 Exhibit L, # 3 Exhibit M, # 4 Exhibit N, # 5 Exhibit O, # 6 Exhibit P, # 7 Exhibit Q)(Anderson, Brian) (Entered: 08/02/2022)
08/02/2022	137	DECLARATION of Monica Chou, Esq. regarding reply, 132 , reply 134 <i>In Support of Motion for Entry of a Temporary Restraining Order</i> (Attachments: # 1 Exhibit K, # 2 Exhibit L, # 3 Exhibit M, # 4 Exhibit N, # 5 Exhibit O, # 6 Exhibit P, # 7 Exhibit Q) (Anderson, Brian) (Entered: 08/02/2022)
08/04/2022	138	MINUTE entry before the Honorable John F. Kness: Telephonic oral argument on the motions for temporary restraining order 109 115 held on 8/4/2022. For the reasons provided on the record, a continued motion hearing is 8/5/2022 at 10:00 AM. The parties are to use the following call-in number: 888-684-8852, conference code 3796759. The public and media representatives may have access to the hearing via the same number. Audio recording of the hearing is not permitted; violations of this prohibition may result in sanctions. Participants are directed to keep their device muted when they are not speaking. Mailed notice (ef,) (Entered: 08/04/2022)
08/05/2022	139	MINUTE entry before the Honorable John F. Kness: Continued telephonic hearing on motions for temporary restraining order 109 115 held on 8/5/2022. As discussed on the record, the parties have agreed to proceed directly to litigating an anticipated preliminary injunction motion by Plaintiffs. The parties will submit a proposed order reflecting this agreed schedule by 8/8/2022. The hearing that was previously set for 8/9/2022 is no longer needed and is stricken. Mailed notice (ef,) (Entered: 08/05/2022)

08/08/2022	140	MINUTE entry before the Honorable John F. Kness: Defendant Nexus Pharmaceuticals, Inc.'s motion for leave to file under seal 125 is granted. Plaintiffs' Motion for leave to file under seal 131 is granted. Mailed notice (ef,) (Entered: 08/08/2022)
08/11/2022	141	ORDER signed by the Honorable John F. Kness on 8/11/2022. Mailed notice(ef,) (Entered: 08/11/2022)
08/11/2022	142	ORDER signed by the Honorable John F. Kness on 8/11/2022: No later than five business days after the date of this Order, Plaintiffs shall deposit the sum of \$2,000,000 (two million dollars), either cash, company check, or surety bond, with the Clerk of the Court until further order of the Court. Mailed notice(ef,) (Entered: 08/12/2022)
08/15/2022	143	MINUTE entry before the Honorable John F. Kness: Per the parties' agreement and for the reasons discussed on the record at the 08/04/2022 hearing, the Court requests that the Executive Committee reassign <i>Melinta Therapeutics, LLC et al. v. Nexus Pharmaceuticals, Inc.</i> , No. 21-cv-5995, to the calendar of this Court under Local Rule 40.4. Mailed notice (ef,) (Entered: 08/15/2022)
08/17/2022	144	SURETY BOND in the amount of \$ \$2,000,000.00 posted by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Document not scanned). (cxr,) (Entered: 08/17/2022)
08/23/2022	145	<p>TRANSCRIPT OF PROCEEDINGS held on 8/4/22 before the Honorable John F. Kness. Order Number: 43890, 43902. Court Reporter Contact Information: Nancy LaBella, nlabella.ilnd@gmail.com, 312-435-6890.</p> <p>IMPORTANT: The transcript may be viewed at the court's public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through the Court Reporter/Transcriber or PACER. For further information on the redaction process, see the Court's web site at www.ilnd.uscourts.gov under Quick Links select Policy Regarding the Availability of Transcripts of Court Proceedings.</p> <p>Redaction Request due 9/13/2022. Redacted Transcript Deadline set for 9/23/2022. Release of Transcript Restriction set for 11/21/2022. (Labella, Nancy) (Entered: 08/23/2022)</p>
08/23/2022	146	<p>TRANSCRIPT OF PROCEEDINGS held on 8/5/22 before the Honorable John F. Kness. Order Number: 43890, 43902. Court Reporter Contact Information: Nancy LaBella, nlabella.ilnd@gmail.com, 312-435-6890.</p> <p>IMPORTANT: The transcript may be viewed at the court's public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through the Court Reporter/Transcriber or PACER. For further information on the redaction process, see the Court's web site at www.ilnd.uscourts.gov under Quick Links select Policy Regarding the Availability of Transcripts of Court Proceedings.</p> <p>Redaction Request due 9/13/2022. Redacted Transcript Deadline set for 9/23/2022. Release of Transcript Restriction set for 11/21/2022. (Labella, Nancy) (Entered: 08/23/2022)</p>
08/25/2022	147	SEALED Brief In Support of a motion for preliminary injunction by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Anderson, Brian) Docket Text Modified on 8/28/2022 (ef,). (Entered: 08/25/2022)

08/25/2022	148	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Declaration of M. Chou In Support of Plaintiffs Motion for Preliminary Injunction</i> (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H, # 9 Exhibit I, # 10 Exhibit J, # 11 Exhibit K, # 12 Exhibit L, # 13 Exhibit R, # 14 Exhibit S, # 15 Exhibit T, # 16 Exhibit U)(Anderson, Brian) (Entered: 08/25/2022)
08/25/2022	149	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Declaration of Tina deVries, Ph.D., In Support Of Plaintiffs' Motion For Preliminary Injunction</i> (Attachments: # 1 Exhibit A, # 2 Exhibit B) (Anderson, Brian) (Entered: 08/25/2022)
08/25/2022	150	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Declaration of Bruce Friedman, M.D. In Support of Plaintiffs' Motion for Preliminary Injunction</i> (Attachments: # 1 Exhibit A, # 2 Exhibit B) (Anderson, Brian) (Entered: 08/25/2022)
08/25/2022	151	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Declaration of John Harlow In Support Of Plaintiffs Motion For Preliminary Injunction</i> (Anderson, Brian) (Entered: 08/25/2022)
08/25/2022	152	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Declaration of Michael E. Tate In Support Of Plaintiffs' Motion For Preliminary Injunction</i> (Attachments: # 1 Exhibit A)(Anderson, Brian) (Entered: 08/25/2022)
08/25/2022	153	PLAINTIFF'S BRIEF in support of a motion for preliminary injunction by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>REDACTED</i> (Anderson, Brian) (Docket Text modified by Clerk's Office) Modified on 8/26/2022 (jmk,). (Entered: 08/25/2022)
08/25/2022	154	DECLARATION regarding Sealed motion 147 , motion for preliminary injunction 153 <i>Declaration of M. Chou In Support of Plaintiffs Motion for Preliminary Injunction REDACTED</i> (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H (REDACTED), # 9 Exhibit I (REDACTED), # 10 Exhibit J (REDACTED), # 11 Exhibit K (REDACTED), # 12 Exhibit L (REDACTED), # 13 Exhibit R, # 14 Exhibit S, # 15 Exhibit T, # 16 Exhibit U) (Anderson, Brian) (Entered: 08/25/2022)
08/25/2022	155	DECLARATION regarding motion for preliminary injunction 153 , Sealed motion 147 <i>Declaration of Tina deVries, Ph.D., In Support Of Plaintiffs' Motion For Preliminary Injunction REDACTED</i> (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Anderson, Brian) (Entered: 08/25/2022)
08/25/2022	156	DECLARATION regarding motion for preliminary injunction 153 , Sealed motion 147 <i>Declaration of Bruce Friedman, M.D. In Support of Plaintiffs' Motion for Preliminary Injunction REDACTED</i> (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Anderson, Brian) (Entered: 08/25/2022)
08/25/2022	157	DECLARATION regarding motion for preliminary injunction 153 , Sealed motion 147 <i>Declaration of John Harlow In Support Of Plaintiffs Motion For Preliminary Injunction REDACTED</i> (Anderson, Brian) (Entered: 08/26/2022)
08/26/2022	158	DECLARATION regarding motion for preliminary injunction 153 , Sealed motion 147 <i>Declaration of Michael E. Tate In Support Of Plaintiffs' Motion For Preliminary Injunction REDACTED</i> (Attachments: # 1 Exhibit A)(Anderson, Brian) (Entered: 08/26/2022)

09/08/2022	159	SEALED REPLY by Nexus Pharmaceuticals, Inc. to SEALED MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Plaintiffs Brief In Support Of A Motion For Preliminary Injunction</i> 147 (Wallace, Joel) (Entered: 09/08/2022)
09/08/2022	160	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Declaration of Joel M. Wallace In Support of Nexus's Opposition to Plaintiffs' Preliminary Injunction Motion</i> (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10, # 11 Exhibit 11, # 12 Exhibit 12, # 13 Exhibit 13, # 14 Exhibit 14)(Wallace, Joel) (Entered: 09/08/2022)
09/08/2022	161	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Declaration of Alexander Klibanov, Ph.D.</i> (Wallace, Joel) (Entered: 09/08/2022)
09/08/2022	162	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Declaration of Henry Chambers, M.D.</i> (Wallace, Joel) (Entered: 09/08/2022)
09/08/2022	163	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Declaration of Ivan Hofmann</i> (Attachments: # 1 Exhibit to Hofmann Declaration)(Wallace, Joel) (Entered: 09/08/2022)
09/08/2022	164	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Declaration of Omair Ahmed</i> (Wallace, Joel) (Entered: 09/08/2022)
09/08/2022	165	RESPONSE by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>to Plaintiffs' Preliminary Injunction Motion (Public)</i> (Wallace, Joel) (Entered: 09/08/2022)
09/08/2022	166	DECLARATION of Joel M. Wallace regarding Response 165 <i>PUBLIC VERSIONS</i> (Attachments: # 1 Exhibit 1 (Redacted), # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4 (Redacted), # 5 Exhibit 5 (Redacted), # 6 Exhibit 6 (Redacted), # 7 Exhibit 7 (Redacted), # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10 (Redacted), # 11 Exhibit 11, # 12 Exhibit 12 (Redacted), # 13 Exhibit 13, # 14 Exhibit 14 (Redacted))(Wallace, Joel) (Entered: 09/08/2022)
09/08/2022	167	DECLARATION of Alexander Klibanov, Ph.D. regarding Response 165 (Wallace, Joel) (Entered: 09/08/2022)
09/08/2022	168	DECLARATION of Henry Chambers, M.D. regarding Response 165 <i>(Public Version)</i> (Wallace, Joel) (Entered: 09/08/2022)
09/08/2022	169	DECLARATION of Ivan Hofmann regarding Response 165 <i>(Public Version)</i> (Attachments: # 1 Exhibit to Hofmann Declaration (Redacted))(Wallace, Joel) (Entered: 09/08/2022)
09/08/2022	170	DECLARATION of Omair Ahmed regarding Response 165 <i>(Public Version)</i> (Wallace, Joel) (Entered: 09/08/2022)
09/15/2022	171	SEALED REPLY by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. to SEALED MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Plaintiffs Brief In Support Of A Motion For Preliminary Injunction</i> 147 (Anderson, Brian) (Entered: 09/15/2022)
09/15/2022	172	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Reply Declaration of Tina deVries, Ph.D. In Support</i>

		<i>of Plaintiffs' Motion for Preliminary Injunction</i> (Attachments: # 1 Exhibit A)(Anderson, Brian) (Entered: 09/15/2022)
09/15/2022	173	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Reply Declaration of Bruce Friedman, M.D. In Support of Plaintiffs' Motion for Preliminary Injunction</i> (Anderson, Brian) (Entered: 09/15/2022)
09/15/2022	174	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Reply Declaration of John Harlow In Support of Plaintiffs' Motion for Preliminary Injunction</i> (Anderson, Brian) (Entered: 09/15/2022)
09/15/2022	175	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Reply Declaration of Michael E. Tate In Support of Plaintiffs' Motion for Preliminary Injunction</i> (Anderson, Brian) (Entered: 09/15/2022)
09/15/2022	176	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>Second Declaration of Monica Chou, Esq. In Support of Plaintiffs' Motion for a Preliminary Injunction</i> (Attachments: # 1 Exhibit V, # 2 Exhibit W, # 3 Exhibit X, # 4 Exhibit Y, # 5 Exhibit Z, # 6 Exhibit AA, # 7 Exhibit BB) (Anderson, Brian) (Entered: 09/15/2022)
09/15/2022	177	DECLARATION of Monica Chou, Esq. regarding reply, 171 <i>Second Declaration of Monica Chou, Esq. In Support of Plaintiffs' Motion for a Preliminary Injunction (Redacted)</i> (Attachments: # 1 Exhibit V, # 2 Exhibit W, # 3 Exhibit X, # 4 Exhibit Y, # 5 Exhibit Z, # 6 Exhibit AA, # 7 Exhibit BB)(Anderson, Brian) (Entered: 09/15/2022)
09/15/2022	178	DECLARATION of Tina deVries, Ph.D. regarding reply, 171 <i>Reply Declaration of Tina deVries, Ph.D. In Support of Plaintiffs' Motion for Preliminary Injunction</i> (Attachments: # 1 Exhibit A)(Anderson, Brian) (Entered: 09/15/2022)
09/15/2022	179	DECLARATION of Bruce Friedman, M.D. regarding reply, 171 <i>Declaration of Bruce Friedman, M.D. In Support of Plaintiffs' Motion for Preliminary Injunction</i> (Anderson, Brian) (Entered: 09/15/2022)
09/15/2022	180	DECLARATION of John Harlow regarding reply, 171 <i>Declaration of John Harlow In Support Of Plaintiffs Motion For Preliminary Injunction</i> (Anderson, Brian) (Entered: 09/15/2022)
09/15/2022	181	DECLARATION of Michael E. Tate regarding reply, 171 <i>Declaration of Michael E. Tate In Support Of Plaintiffs' Motion For Preliminary Injunction</i> (Anderson, Brian) (Entered: 09/15/2022)
09/15/2022	182	REPLY by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. to reply, 171 <i>Plaintiffs' Reply Brief In Support Of A Motion For Preliminary Injunction (REDACTED)</i> (Anderson, Brian) (Entered: 09/15/2022)
09/23/2022	183	STATUS Report <i>Joint Status Report</i> by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Anderson, Brian) (Entered: 09/23/2022)
09/28/2022	184	MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. for extension of time <i>for Expert Discovery</i> (Wallace, Joel) (Entered: 09/28/2022)
09/28/2022	185	MINUTE entry before the Honorable Maria Valdez: Plaintiff's response to Defendant's Opposed Motion to Amend Scheduling Order 184 is due by 10/3/22, and Defendant's reply, if any, is due by 10/7/22. The parties are strongly encouraged to resolve their dispute without the need for judicial intervention. Mailed notice (lp,) (Entered: 09/28/2022)

10/04/2022	186	MINUTE entry before the Honorable Maria Valdez: The parties' Joint Stipulation and Order to Extend Time is entered, and the expert schedule is amended as follows: the deadline for the opening expert reports on issues for which either party bears the burden of proof or production is extended to 10/31/22; the deadline for rebuttal expert reports is extended to 12/12/22; and the close of expert discovery is extended to 1/25/23. Defendant's Opposed Motion to Amend Scheduling Order 184 is denied as moot. Mailed notice (lp,) (Entered: 10/04/2022)
10/04/2022	187	JOINT STIPULATION and ORDER TO EXTEND TIME. Signed by the Honorable Maria Valdez on 10/4/2022:Mailed notice (lp,) (Entered: 10/04/2022)
10/11/2022	188	MINUTE entry before the Honorable John F. Kness: A telephonic status hearing is set for 10/13/2022 at 11:00 a.m. At the hearing, the parties should be prepared to discuss with the Court the effect on this case (if any) of the 10/7/2022 order of the United States District Court for the District of Columbia in the related matter Melinta Therapeutics, LLC, et. al, v. FDA, et. al, No. CV 22-2190 (RC), 2022 WL 6100188, Dkt. 34, (D.D.C. Oct. 7, 2022). Further instructions on how to dial in for the telephonic hearing will be provided by separate order. Mailed notice (jk) (Entered: 10/11/2022)
10/11/2022	189	STATUS Report <i>Joint Status Report</i> by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Attachments: # 1 Exhibit A, # 2 Exhibit B) (Anderson, Brian) (Entered: 10/11/2022)
10/12/2022	190	MINUTE entry before the Honorable John F. Kness: For the 10/13/2022 status hearing, the parties are to use the following call-in number: 888-684-8852, conference code 3796759. The public and media representatives may have access to the hearing via the same number. Audio recording of the hearing is not permitted; violations of this prohibition may result in sanctions. Participants are directed to keep their device muted when they are not speaking. Mailed notice (ef,) (Entered: 10/12/2022)
10/13/2022	191	MOTION by Attorney Brian N. Anderson to withdraw as attorney for Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc.. No party information provided (Anderson, Brian) (Entered: 10/13/2022)
10/13/2022	192	MINUTE entry before the Honorable John F. Kness: Telephonic status hearing held on 10/13/2022. For the reasons provided on the record, rulings on Plaintiffs' request for a preliminary injunction and Defendant's motion 39 to dismiss Count I are stayed pending resolution of the related action in the District of Columbia. At their joint request, the parties will meet and confer on potential trial dates The Courtroom Deputy will contact the parties regarding possible trial dates and the parties shall promptly respond to the Courtroom Deputy with their availability and any conflicts. A new status hearing date will be set by separate order. Mailed notice (ef,) (Entered: 10/13/2022)
10/13/2022	193	MINUTE entry before the Honorable John F. Kness: Motion by counsel to withdraw as attorney 191 is granted. Attorney Brian Neil Anderson is withdrawn as counsel. Mailed notice (ef,) (Entered: 10/13/2022)
11/11/2022	194	MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. for summary judgment of <i>Non-Infringement</i> (Wallace, Joel) (Entered: 11/11/2022)
11/11/2022	195	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Brief in Support of Nexus's Motion for Summary Judgment of Non-Infringement</i> (Wallace, Joel) (Entered: 11/11/2022)
11/11/2022	196	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Rule 56.1 Statement of Material Facts</i> (Attachments: # 1 Declaration of Joel Wallace, # 2 Exhibit A, # 3 Exhibit B, # 4 Exhibit C, # 5 Exhibit D, #

		6 Exhibit E, # 7 Exhibit F, # 8 Exhibit G, # 9 Exhibit H)(Wallace, Joel) (Entered: 11/11/2022)
11/11/2022	197	MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. to seal document sealed document 195 , sealed document, 196 <i>Unopposed</i> (Wallace, Joel) (Entered: 11/11/2022)
11/11/2022	198	MEMORANDUM by Nexus Pharmaceuticals, Inc. in support of motion for summary judgment 194 <i>Public Version</i> (Wallace, Joel) (Entered: 11/11/2022)
11/11/2022	199	RULE 56 (a) Statement by Nexus Pharmaceuticals, Inc. regarding motion for summary judgment 194 <i>PUBLIC VERSIONS</i> (Attachments: # 1 Declaration of Joel Wallace, # 2 Exhibit A - FILED UNDER SEAL, # 3 Exhibit B - FILED UNDER SEAL, # 4 Exhibit C, # 5 Exhibit D - FILED UNDER SEAL, # 6 Exhibit E - FILED UNDER SEAL, # 7 Exhibit F, # 8 Exhibit G - FILED UNDER SEAL, # 9 Exhibit H)(Wallace, Joel) (Entered: 11/11/2022)
11/14/2022	200	Joint Statement Regarding Briefing Schedule for Nexus's Motion for Summary Judgment STATEMENT by Nexus Pharmaceuticals, Inc. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C)(Wallace, Joel) (Entered: 11/14/2022)
11/21/2022	201	MINUTE entry before the Honorable John F. Kness: By agreement of the parties, this case is set for a one-week bench trial on 6/6/2023 at 09:00 AM. Pretrial conference set for 5/30/2023 at 01:30 PM. Mailed notice (ef,) (Entered: 11/21/2022)
12/29/2022	202	ANNUAL REMINDER: Pursuant to Local Rule 3.2 (Notification of Affiliates) , any nongovernmental party, other than an individual or sole proprietorship, must file a statement identifying all its affiliates known to the party after diligent review or, if the party has identified no affiliates, then a statement reflecting that fact must be filed. An affiliate is defined as follows: any entity or individual owning, directly or indirectly (through ownership of one or more other entities), 5% or more of a party. The statement is to be electronically filed as a PDF in conjunction with entering the affiliates in CM/ECF as prompted. As a reminder to counsel, parties must supplement their statements of affiliates within thirty (30) days of any change in the information previously reported. This minute order is being issued to all counsel of record to remind counsel of their obligation to provide updated information as to additional affiliates if such updating is necessary. If counsel has any questions regarding this process, this LINK will provide additional information. Signed by the Executive Committee on 12/29/2022: Mailed notice. (tg,) (Entered: 12/30/2022)
01/19/2023	203	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for extension of time <i>to complete expert discovery (Joint Motion)</i> (Deming, Mark) (Entered: 01/19/2023)
02/14/2023	204	STATUS Report by Nexus Pharmaceuticals, Inc. (Attachments: # 1 Exhibit 1)(Wallace, Joel) (Entered: 02/14/2023)
02/15/2023	205	MINUTE entry before the Honorable Maria Valdez: The parties' Joint Motion to Extend Expert Discovery Deadline 203 is granted. All matters related to the referral of this action having been resolved, the case is returned to the assigned judge. Mailed notice. (exr,) (Entered: 02/15/2023)
03/15/2023	206	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for release of bond obligation (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C)(Deming, Mark) (Entered: 03/15/2023)
03/16/2023	207	Briefing Schedules for D.I. 206 Motion to Release Bond STATEMENT by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Deming,

		Mark) (Entered: 03/16/2023)
03/19/2023	208	MINUTE entry before the Honorable John F. Kness: Before the Court is Plaintiffs' Opposed Motion to Release Bond 206 , for which the parties have proposed competing briefing schedules 207 . Because both proposals are unreasonable, the following schedule will apply: any response in opposition to the Motion to Release Bond 206 must be filed on or before 4/3/2023. Any reply in support of the motion must be filed on or before 4/10/2023. No extensions. Mailed notice (jk) (Entered: 03/19/2023)
03/21/2023	209	MOTION for Leave to Appear Pro Hac Vice Filing fee \$ 150, receipt number AILNDC-20459289. (Austin, Erin) (Entered: 03/21/2023)
03/21/2023	210	MOTION for Leave to Appear Pro Hac Vice Filing fee \$ 150, receipt number AILNDC-20459389. (Yang, Jerri) (Entered: 03/21/2023)
03/21/2023	211	MINUTE entry before the Honorable John F. Kness: Motions by counsel for leave to appear pro hac vice 209 210 are granted. Mailed notice (ef,) (Entered: 03/21/2023)
03/22/2023	212	ATTORNEY Appearance for Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. by Matthew Thomas Wilkerson (Wilkerson, Matthew) (Entered: 03/22/2023)
03/23/2023	213	NOTICE by Monica Chou of Change of Address (Chou, Monica) (Entered: 03/23/2023)
03/23/2023	214	NOTICE by Dominick A Conde of Change of Address (Conde, Dominick) (Entered: 03/23/2023)
03/23/2023	215	NOTICE by Ha Kung Wong of Change of Address (Wong, Ha Kung) (Entered: 03/23/2023)
03/23/2023	216	NOTICE by Damien Noel Dombrowski of Change of Address (Dombrowski, Damien) (Entered: 03/23/2023)
03/23/2023	217	NOTICE by Monica Chou of Change of Address (Chou, Monica) (Entered: 03/23/2023)
04/03/2023	218	MOTION for Leave to Appear Pro Hac Vice Filing fee \$ 150, receipt number AILNDC-20503251. (Wilkerson, Matthew) (Entered: 04/03/2023)
04/03/2023	219	RESPONSE by Nexus Pharmaceuticals, Inc.in Opposition to MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. for release of bond obligation 206 (Wilkerson, Matthew) (Entered: 04/03/2023)
04/04/2023	220	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. Joint Motion for Entry of Schedule for Preparation of Pretrial Order (Deming, Mark) (Entered: 04/04/2023)
04/05/2023	221	MINUTE entry before the Honorable John F. Kness: Motion by counsel for leave to appear pro hac vice 218 is granted. Mailed notice (ef,) (Entered: 04/05/2023)
04/06/2023	222	MINUTE entry before the Honorable John F. Kness: Joint motion for entry of pretrial schedule 220 is granted. The schedule set forth in the parties' motion shall govern. Plaintiffs' request to submit trial briefs is granted over Defendant's objection. Parties to submit draft trial briefs to one another on or before 5/12/2023 and must meet and confer on or about 5/15/2023. Parties must submit a short joint status report following their meet-and-confer on or before 5/19/2023. Mailed notice (ef,) (Entered: 04/06/2023)
04/10/2023	223	REPLY by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. to motion for release of bond obligation 206 (Attachments: # 1 Exhibit A)(Deming, Mark) (Entered: 04/10/2023)

04/25/2023		Bench Trial set for 6/6/2023, 6/7/2023, 6/8/2023, 6/9/2023. (ef,) (Entered: 04/25/2023)
05/16/2023	<u>224</u>	SEALED MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Motion in Limine to Exclude New Opinions</i> (Attachments: # <u>1</u> Exhibit Ex. A Opening Expert Report of Dr. Friedman, # <u>2</u> Exhibit Ex. B Opening Expert Report of Dr. DeVries, # <u>3</u> Errata Ex. C Deposition Transcript of Dr. Friedman) (Wilkerson, Matthew) (Entered: 05/16/2023)
05/16/2023	<u>225</u>	SEALED MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Motion to Seal Dkt. Entry No. 224</i> (Wilkerson, Matthew) (Entered: 05/16/2023)
05/16/2023	<u>226</u>	SEALED PRETRIAL Brief by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. (Wilkerson, Matthew) Modified on 9/19/2023 (ef,). (Entered: 05/16/2023)
05/16/2023	<u>227</u>	SEALED MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Motion to Seal Dkt. Entry No. 226</i> (Wilkerson, Matthew) (Entered: 05/16/2023)
05/16/2023	<u>228</u>	PROPOSED Pretrial Order (<i>Joint</i>) (Attachments: # <u>1</u> Exhibit 1, # <u>2</u> Exhibit 2 (Redacted), # <u>3</u> Exhibit 3, # <u>4</u> Exhibit 4)(Deming, Mark) (Entered: 05/16/2023)
05/16/2023	<u>229</u>	MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc.in limine (<i>Public Version</i>) (Attachments: # <u>1</u> Exhibit A (Redacted), # <u>2</u> Exhibit B (Redacted), # <u>3</u> Exhibit C (Redacted), # <u>4</u> Exhibit D (Redacted), # <u>5</u> Exhibit E (Redacted))(Deming, Mark) Modified on 3/25/2024 (exr,). (Entered: 05/16/2023)
05/16/2023	<u>230</u>	TRIAL Brief (<i>Public Version</i>) by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Attachments: # <u>1</u> Exhibit A (Redacted))(Deming, Mark) (Entered: 05/16/2023)
05/16/2023	<u>231</u>	SEALED MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>re Plaintiffs' Motion in Limine DI 229</i> (Attachments: # <u>1</u> Exhibit A, # <u>2</u> Exhibit B, # <u>3</u> Exhibit C, # <u>4</u> Exhibit D, # <u>5</u> Exhibit E)(Deming, Mark) (Entered: 05/16/2023)
05/16/2023	<u>232</u>	SEALED MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>re Exhibit 2 to Joint Proposed Pretrial Order DI 228</i> (Attachments: # <u>1</u> Exhibit 2)(Deming, Mark) (Entered: 05/16/2023)
05/16/2023	<u>233</u>	SEALED MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>re Plaintiffs' Trial Brief DI 230</i> (Attachments: # <u>1</u> Plaintiffs' Trial Brief, # <u>2</u> Exhibit A)(Deming, Mark) (Entered: 05/16/2023)
05/19/2023	<u>234</u>	STATUS Report (<i>Joint</i>) by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Deming, Mark) (Entered: 05/19/2023)
05/23/2023	<u>235</u>	RESPONSE by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. in limine to Plaintiffs' Motion in Limine (Wilkerson, Matthew) Docket Text Modified on 6/1/2023 (ef,). (Entered: 05/23/2023)
05/23/2023	<u>236</u>	RESPONSE by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc.in Opposition to SEALED MOTION by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Motion in Limine to</i>

		<i>Exclude New Opinions</i> 224 (Public Version) (Attachments: # 1 Exhibit A (Redacted), # 2 Exhibit B (Redacted), # 3 Exhibit C (Redacted))(Deming, Mark) (Entered: 05/23/2023)
05/23/2023	237	SEALED MOTION by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. <i>re Plaintiffs' Opposition to Defendant's Motion in Limine DI 236</i> (Attachments: # 1 Opposition Brief, # 2 Exhibit A, # 3 Exhibit B, # 4 Exhibit C) (Deming, Mark) (Entered: 05/23/2023)
05/30/2023	238	MINUTE entry before the Honorable John F. Kness: Final pretrial conference hearing held on 5/30/2023. Oral motion to dismiss Count 1 with prejudice is granted. Further relief to be provided by separate order. Mailed notice (smm) (Entered: 05/31/2023)
06/02/2023	239	ORDER signed by the Honorable John F. Kness on 6/2/2023: The motion in limine of Defendant Nexus Pharmaceuticals (Dkt. 224) to exclude new expert opinions on infringement is denied. Plaintiffs' motion to release bond (Dkt. 206) is granted. See accompanying statement for details. Mailed notice(ef,) (Entered: 06/02/2023)
06/06/2023	240	MINUTE entry before the Honorable John F. Kness: Before the Court are various motions to seal the parties' pretrial motions and filings 225 227 231 232 233 . For the reasons stated in the briefing, the motions are granted. To the extent the parties have not already done so, they are directed to file public-facing versions of each sealed filing with only the sensitive information identified in the protective order 102 redacted. Mailed notice (ef,) (Entered: 06/06/2023)
06/06/2023	241	MINUTE entry before the Honorable John F. Kness: Bench Trial began. Bench Trial continued to 6/7/2023 at 08:30 AM. Mailed notice (ef,) (Entered: 06/07/2023)
06/07/2023	242	MINUTE entry before the Honorable John F. Kness: Bench trial held and continued to 6/8/2023 at 09:00 AM. Mailed notice (ef,) (Entered: 06/08/2023)
06/08/2023	243	MINUTE entry before the Honorable John F. Kness: Bench trial held and continued to 6/9/2023 at 8:30 AM. Mailed notice (ef,) (Entered: 06/09/2023)
06/09/2023	244	MINUTE entry before the Honorable John F. Kness: Bench trial held and evidence completed on 6/9/2023. On or before 6/16/2023, the parties must: (1) meet and confer concerning a schedule to govern post-trial briefing; (2) file a joint statement on the docket setting forth the agreed proposed schedule (or proposed competing schedules); and (3) submit a Word version of their proposed scheduling order (or competing proposals, if the parties cannot agree) to the Court's proposed order mailbox, Proposed_Order_Kness@ilnd.uscourts.gov. Proposed_Order_Kness@ilnd.uscourts.gov. A telephonic hearing for case tracking purposes only is set for 6/29/2023 at 10:00 AM. The parties are to use the following call-in number: 888-684-8852, conference code 3796759. The public and media representatives may have access to the hearing via the same number. Audio recording of the hearing is not permitted; violations of this prohibition may result in sanctions. Participants are directed to keep their device muted when they are not speaking. Mailed notice (ef,) (Entered: 06/12/2023)
06/16/2023	245	Joint Statement Regarding Post-Trial Briefing STATEMENT by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Attachments: # 1 Text of Proposed Order)(Deming, Mark) (Entered: 06/16/2023)
06/22/2023	246	MINUTE entry before the Honorable John F. Kness: On 6/16/2023, the parties filed a joint statement regarding post-trial briefing 245 . The joint statement included a scheduling order to govern post-trial briefing. Having reviewed the parties' proposal and finding it reasonable, the Court adopts it with one change: closing arguments are set for 8/15/2023 at 8:30 a.m. to accommodate the Court's trial schedule. Enter separate scheduling order. The hearing set for 6/29/2023 is stricken. Mailed notice (ef,) (Entered: 06/22/2023)

06/22/2023	247	ORDER signed by the Honorable John F. Kness on 6/22/2023. Mailed notice(ef,) (Entered: 06/22/2023)
07/12/2023	248	Opening Post-Trial Brief by Nexus Pharmaceuticals, Inc. (Attachments: # 1 Exhibit Ex. A 2/21/22 Email)(Wilkerson, Matthew) (Entered: 07/12/2023)
07/12/2023	249	Opening Post-Trial Brief by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Deming, Mark) (Entered: 07/12/2023)
07/13/2023	250	Defendant Nexus's Corrected Opening Post-Trial Brief by Nexus Pharmaceuticals, Inc. (Attachments: # 1 Exhibit Ex. A 2/21/22 Email)(Wilkerson, Matthew) (Entered: 07/13/2023)
07/26/2023	251	Responsive Post-Trial Brief by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Deming, Mark) (Entered: 07/26/2023)
07/26/2023	252	Proposed Findings of Fact by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Deming, Mark) (Entered: 07/26/2023)
07/26/2023	253	Proposed Conclusions of Law by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Deming, Mark) (Entered: 07/26/2023)
07/26/2023	254	Defendant Nexus's Responsive Post-Trial Brief by Nexus Pharmaceuticals, Inc. (Wilkerson, Matthew) (Entered: 07/26/2023)
07/26/2023	255	Defendant Nexus's Proposed Findings of Fact and Conclusions of Law by Nexus Pharmaceuticals, Inc. (Wilkerson, Matthew) (Entered: 07/26/2023)
08/15/2023	256	MINUTE entry before the Honorable John F. Kness: In-Person Closing Arguments heard on 8/15/2023. This matter is taken under advisement; ruling by mail. Mailed notice (ef,) (Entered: 08/17/2023)
09/19/2023	257	MINUTE entry before the Honorable John F. Kness: This case remains before the Court for adjudication of the recently-completed bench trial, post-trial briefing, and closing arguments. The Court expects to issue its findings of fact and conclusions of law under FRCP 52(a)(1) within the first or second week of October 2023. In view of the completed trial, Defendant's motion 184 for an extension of time to complete expert discovery and motion 194 for summary judgment of noninfringement are dismissed as moot. Defendant's unopposed motion 197 to submit a sealed filing is granted. Plaintiffs' separate unopposed motion 237 to submit a sealed filing is granted. Any other pending motions will be addressed separately or as part of the Court's merits ruling. Mailed notice (ef,) (Entered: 09/19/2023)
10/25/2023	258	MINUTE entry before the Honorable John F. Kness: A telephonic hearing is set for 11/8/2023 at 09:50 AM. The parties are to use the following call-in number: 888-684-8852, conference code 3796759. The public and media representatives may have access to the hearing via the same number. Audio recording of the hearing is not permitted; violations of this prohibition may result in sanctions. Participants are directed to keep their device muted when they are not speaking. Mailed notice (ef,) (Entered: 10/25/2023)
11/13/2023	259	MINUTE entry before the Honorable John F. Kness: Telephonic status hearing held on 11/8/2023. Ruling to issue by mail. Mailed notice (ags) (Entered: 11/13/2023)
12/28/2023	260	ANNUAL REMINDER: Pursuant to Local Rule 3.2 (Notification of Affiliates) , any nongovernmental party, other than an individual or sole proprietorship, must file a statement identifying all its affiliates known to the party after diligent review or, if the party has identified no affiliates, then a statement reflecting that fact must be filed. An affiliate is defined as follows: any entity or individual owning, directly or indirectly (through ownership of one or more other entities), 5% or more of a party. The statement is

		to be electronically filed as a PDF in conjunction with entering the affiliates in CM/ECF as prompted. As a reminder to counsel, parties must supplement their statements of affiliates within thirty (30) days of any change in the information previously reported. This minute order is being issued to all counsel of record to remind counsel of their obligation to provide updated information as to additional affiliates if such updating is necessary. If counsel has any questions regarding this process, this LINK will provide additional information. Signed by the Executive Committee on 12/28/2023: Mailed notice. (tg,) (Entered: 12/28/2023)
01/31/2024	261	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Status Update</i> (Attachments: # 1 Exhibit 1)(Wallace, Joel) (Entered: 01/31/2024)
02/02/2024	262	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (<i>Response to Status Update</i>) (Attachments: # 1 Exhibit A)(Deming, Mark) (Entered: 02/02/2024)
02/20/2024	263	SEALED DOCUMENT by Plaintiffs Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (<i>Further Status Update</i>) (Deming, Mark) (Entered: 02/20/2024)
02/21/2024	264	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Status Report</i> (Wallace, Joel) (Entered: 02/21/2024)
02/23/2024	265	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. <i>Status Report</i> (Wallace, Joel) (Entered: 02/23/2024)
04/22/2024	266	MINUTE entry before the Honorable John F. Kness: A telephonic hearing is set for 5/13/2024 at 10:00 A.M. The parties are to use the following call-in number: 888-684-8852, conference code 3796759. The public and media representatives may have access to the hearing via the same number. Audio recording of the hearing is not permitted; violations of this prohibition may result in sanctions. Participants are directed to keep their device muted when they are not speaking. Mailed notice. (exr,) (Entered: 04/22/2024)
04/23/2024	267	MINUTE entry before the Honorable John F. Kness: Docket Entry 266 was entered in error. A telephonic hearing is set for 5/30/2024 at 9:30 A.M. The parties are to use the following call-in number: 888-684-8852, conference code 3796759. The public and media representatives may have access to the hearing via the same number. Audio recording of the hearing is not permitted; violations of this prohibition may result in sanctions. Participants are directed to keep their device muted when they are not speaking. Mailed notice. (exr,) (Entered: 04/23/2024)
05/21/2024	268	Letter to Judge Kness re Filing of Related Case by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Deming, Mark) (Entered: 05/21/2024)
05/24/2024	269	STATUS Report by Nexus Pharmaceuticals, Inc. (Wallace, Joel) (Entered: 05/24/2024)
05/30/2024	270	MINUTE entry before the Honorable John F. Kness: Telephonic status hearing held 5/30/2024. As discussed on the record, the parties addressed the new case (24-cv-04180) as to the same parties and whether it would have any effect on this earlier-filed case. As noted, the post-trial decision is forthcoming. Mailed notice. (exr,) (Entered: 05/31/2024)
10/28/2024	271	SEALED DOCUMENT by Plaintiffs Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc., Counter Defendant Melinta Subsidiary Corp. (<i>Letter</i>) (Deming,

		Mark) (Entered: 10/28/2024)
10/29/2024	272	SEALED DOCUMENT by Counter Claimant Nexus Pharmaceuticals, Inc., Defendant Nexus Pharmaceuticals, Inc. (Nelson, Kevin) (Entered: 10/29/2024)
11/01/2024	273	MINUTE entry before the Honorable John F. Kness: A telephonic status hearing is set for 11/15/2024 at 9:00 am. With regret for the delay, the Court anticipates issuing its required findings of fact and conclusions of law under Rule 52 of the Federal Rules of Civil Procedure either in advance of that hearing date or at the hearing. Mailed notice. (exr,) (Entered: 11/01/2024)
11/14/2024	274	MINUTE entry before the Honorable John F. Kness: The hearing set for 11/15/2024 is stricken as unnecessary, as substantive relief will be entered by separate order that same day. Mailed notice. (exr,) (Entered: 11/14/2024)
11/15/2024	275	MINUTE entry before the Honorable John F. Kness: For the reasons stated in the accompanying opinion, which shall serve as the Court's required findings of fact and conclusions of law under Rule 52 of the Federal Rules of Civil Procedure, the Court holds that Plaintiffs have proven by a preponderance of the evidence that Defendant has infringed on its patents (Counts II and III), and Defendant has failed to prove by clear and convincing evidence that Plaintiffs' patents are invalid (Counts I and II of the counterclaim). Count I of the Complaint is dismissed as moot. Enter separate findings of fact and conclusions of law. Enter separate final judgment order with an appended permanent injunction order. The Court offers its sincere gratitude to counsel for both parties for their well-presented arguments. Civil case terminated. Mailed notice. (exr,) (Entered: 11/15/2024)
11/15/2024	276	FINDINGS OF FACT AND CONCLUSIONS OF LAW signed by the Honorable John F. Kness on 11/15/2024. Mailed notice. (exr,) (Entered: 11/15/2024)
11/15/2024	277	ENTERED JUDGMENT. Mailed notice. (exr,) (Entered: 11/15/2024)
12/09/2024	278	NOTICE of appeal by Nexus Pharmaceuticals, Inc. regarding orders 277 Filing fee \$ 605, receipt number AILNDC-22818173. Receipt number: n (Ji, Helen) (Entered: 12/09/2024)
12/10/2024		ENTERED IN ERROR. (jn,) Modified on 12/10/2024 (jn,). (Entered: 12/10/2024)
12/10/2024	279	ENTERED IN ERROR. (jn,) Modified on 12/10/2024 (jn,). (Entered: 12/10/2024)
12/10/2024	280	TRANSMITTED to the Federal Circuit the short record on notice of appeal 278 . Notified counsel. (jn,) (Entered: 12/10/2024)
12/10/2024	281	NOTICE of Correction regarding document number 279 . (jn,) Modified on 12/10/2024 (jn,). (Entered: 12/10/2024)
12/13/2024	282	ACKNOWLEDGMENT of receipt of short record on appeal regarding notice of appeal 278 ; USCA for the Federal Circuit Docket No. 2025-1281 (jxm,) (Entered: 12/16/2024)
12/23/2024	283	TRANSCRIPT OF PROCEEDINGS held on 6/6/23 before the Honorable John F. Kness. Trial, Volume 1. Court Reporter Contact Information: Nancy LaBella, Nancy_LaBella@ilnd.uscourts.gov, 312-435-6890. IMPORTANT: The transcript may be viewed at the court's public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through the Court Reporter/Transcriber or PACER. For further information on the redaction process, see the Court's web site at www.ilnd.uscourts.gov under Quick Links select Policy Regarding the Availability of Transcripts of Court Proceedings.

		Redaction Request due 1/13/2025. Redacted Transcript Deadline set for 1/23/2025. Release of Transcript Restriction set for 3/24/2025. (Labella, Nancy) (Entered: 12/23/2024)
12/23/2024	<u>284</u>	<p>TRANSCRIPT OF PROCEEDINGS held on 6/7/23 before the Honorable John F. Kness. Trial Volume 2. Court Reporter Contact Information: Nancy LaBella, Nancy_LaBella@ilnd.uscourts.gov, 312-435-6890.</p> <p>IMPORTANT: The transcript may be viewed at the court's public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through the Court Reporter/Transcriber or PACER. For further information on the redaction process, see the Court's web site at www.ilnd.uscourts.gov under Quick Links select Policy Regarding the Availability of Transcripts of Court Proceedings.</p> <p>Redaction Request due 1/13/2025. Redacted Transcript Deadline set for 1/23/2025. Release of Transcript Restriction set for 3/24/2025. (Labella, Nancy) (Entered: 12/23/2024)</p>
12/23/2024	<u>285</u>	<p>TRANSCRIPT OF PROCEEDINGS held on 6/8/23 before the Honorable John F. Kness. Trial Volume 3. Court Reporter Contact Information: Nancy LaBella, Nancy_LaBella@ilnd.uscourts.gov, 312-435-6890.</p> <p>IMPORTANT: The transcript may be viewed at the court's public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through the Court Reporter/Transcriber or PACER. For further information on the redaction process, see the Court's web site at www.ilnd.uscourts.gov under Quick Links select Policy Regarding the Availability of Transcripts of Court Proceedings.</p> <p>Redaction Request due 1/13/2025. Redacted Transcript Deadline set for 1/23/2025. Release of Transcript Restriction set for 3/24/2025. (Labella, Nancy) (Entered: 12/23/2024)</p>
12/23/2024	<u>286</u>	<p>TRANSCRIPT OF PROCEEDINGS held on 6/9/23 before the Honorable John F. Kness. Trial Volume 4. Court Reporter Contact Information: Nancy LaBella, Nancy_LaBella@ilnd.uscourts.gov, 312-435-6890.</p> <p>IMPORTANT: The transcript may be viewed at the court's public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through the Court Reporter/Transcriber or PACER. For further information on the redaction process, see the Court's web site at www.ilnd.uscourts.gov under Quick Links select Policy Regarding the Availability of Transcripts of Court Proceedings.</p> <p>Redaction Request due 1/13/2025. Redacted Transcript Deadline set for 1/23/2025. Release of Transcript Restriction set for 3/24/2025. (Labella, Nancy) (Entered: 12/23/2024)</p>
12/23/2024	<u>287</u>	<p>TRANSCRIPT OF PROCEEDINGS held on 8/15/23 before the Honorable John F. Kness. Trial Volume 5. Court Reporter Contact Information: Nancy LaBella, Nancy_LaBella@ilnd.uscourts.gov, 312-435-6890.</p> <p>IMPORTANT: The transcript may be viewed at the court's public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through the Court Reporter/Transcriber or PACER. For further information on the redaction process, see the Court's web site at www.ilnd.uscourts.gov under Quick Links select Policy Regarding the Availability of Transcripts of Court Proceedings.</p>

PACER. For further information on the redaction process, see the Court's web site at www.ilnd.uscourts.gov under Quick Links select Policy Regarding the Availability of Transcripts of Court Proceedings.

Redaction Request due 1/13/2025. Redacted Transcript Deadline set for 1/23/2025. Release of Transcript Restriction set for 3/24/2025. (Labella, Nancy) (Entered: 12/23/2024)

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APPEAL,INTERDIST - TRANSF,JANTZ,TERMED

United States District Court
Northern District of Illinois - CM/ECF NextGen 1.8 (rev. 1.8.2) (Chicago)
CIVIL DOCKET FOR CASE #: 1:21-cv-05995

Melinta Therapeutics, LLC et al v. Nexus Pharmaceuticals, Inc.

Assigned to: Honorable John F. Kness

Lead case: [1:21-cv-02636](#)Member case: [\(View Member Case\)](#)related Case: [1:21-cv-02636](#)

Case in other court: 25-01282

New Jersey, 2:21-cv-11198

Cause: 35:271 Patent Infringement

Date Filed: 11/09/2021

Date Terminated: 11/15/2024

Jury Demand: None

Nature of Suit: 835 Patent - Abbreviated

New Drug Application(ANDA)

Jurisdiction: Federal Question

Plaintiff**Melinta Therapeutics, LLC**

represented by **LIZA M. WALSH**
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APPX000228

Plaintiff**Melinta Subsidiary Corp.**

represented by **LIZA M. WALSH**
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ATTORNEY TO BE NOTICED

Brian Neil Anderson
(See above for address)
ATTORNEY TO BE NOTICED

WILLIAM T. WALSH , JR
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Plaintiff**Rempex Pharmaceuticals, Inc.**

represented by **LIZA M. WALSH**
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Brian Neil Anderson
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WILLIAM T. WALSH , JR
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V.

Defendant**Nexus pharmaceuticals, Inc.**

represented by **James S. Richter**
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Defendant

Imron T Aly
PHV

Defendant

Joel M Wallace
PHV

Defendant

Ha Kung Wong*PHV***Defendant****Damien N Dombrowski***PHV***Defendant****Monica Shou***PHV*

Date Filed	#	Docket Text
05/13/2021	<u>1</u>	COMPLAINT against NEXUS PHARMACEUTICALS, INC. (Filing and Admin fee \$ 402 receipt number ANJDC-12461448), filed by MELINTA THERAPEUTICS, LLC, REMPEX PHARMACEUTICALS, INC., MELINTA SUBSIDIARY CORP.. (Attachments: # <u>1</u> Exhibit A-D, # <u>2</u> Civil Cover Sheet, # <u>3</u> AO120 Form)(WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 05/13/2021)
05/13/2021	<u>2</u>	Corporate Disclosure Statement by MELINTA SUBSIDIARY CORP., MELINTA THERAPEUTICS, LLC, REMPEX PHARMACEUTICALS, INC.. (WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 05/13/2021)
05/14/2021		Judge Brian R. Martinotti and Magistrate Judge Andre M. Espinosa added. (ps) [Transferred from New Jersey on 11/9/2021.] (Entered: 05/14/2021)
05/14/2021	<u>3</u>	SUMMONS ISSUED as to NEXUS PHARMACEUTICALS, INC. Attached is the official court Summons, please fill out Defendant and Plaintiffs attorney information and serve. (jc,) [Transferred from New Jersey on 11/9/2021.] (Entered: 05/14/2021)
05/14/2021	<u>4</u>	AO120 Patent/Trademark Form filed. (Attachments: # <u>1</u> Complaint and Exhibits) (jc,) [Transferred from New Jersey on 11/9/2021.] (Entered: 05/14/2021)
05/18/2021	<u>5</u>	NOTICE of Appearance by WILLIAM T. WALSH, JR on behalf of MELINTA SUBSIDIARY CORP., MELINTA THERAPEUTICS, LLC, REMPEX PHARMACEUTICALS, INC. (WALSH, WILLIAM) [Transferred from New Jersey on 11/9/2021.] (Entered: 05/18/2021)
06/02/2021	<u>6</u>	SUMMONS Returned Executed by MELINTA THERAPEUTICS, LLC, REMPEX PHARMACEUTICALS, INC., MELINTA SUBSIDIARY CORP.. NEXUS PHARMACEUTICALS, INC. served on 5/27/2021, answer due 6/17/2021. (WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 06/02/2021)
06/15/2021	<u>7</u>	NOTICE of Appearance by JAMES S. RICHTER on behalf of NEXUS PHARMACEUTICALS, INC. (RICHTER, JAMES) [Transferred from New Jersey on 11/9/2021.] (Entered: 06/15/2021)
06/15/2021	<u>8</u>	Application and Proposed Order for Clerk's Order to extend time to answer as to Defendant Nexus Pharmaceuticals, Inc... (RICHTER, JAMES) [Transferred from New Jersey on 11/9/2021.] (Entered: 06/15/2021)
06/16/2021		Clerk`s Text Order - The <u>8</u> Application for Clerk's Order to Ext Answer/Proposed Order submitted by NEXUS PHARMACEUTICALS, INC. has been GRANTED. The answer due date has been set for 7/1/2021. (jc,) [Transferred from New Jersey on 11/9/2021.] (Entered: 06/16/2021)

07/01/2021	9	MOTION to Dismiss <i>pursuant to Fed.R.Civ.P. 12(b)(3) and to transfer venue</i> by NEXUS PHARMACEUTICALS, INC.. (Attachments: # 1 Brief, # 2 Declaration of James Richter with Exhibits, # 3 Text of Proposed Order)(RICHTER, JAMES) [Transferred from New Jersey on 11/9/2021.] (Entered: 07/01/2021)
07/06/2021		Set Deadlines as to 9 MOTION to Dismiss <i>pursuant to Fed.R.Civ.P. 12(b)(3) and to transfer venue</i> . Motion set for 8/2/2021 before Judge Brian R. Martinotti. Unless otherwise directed by the Court, this motion will be decided on the papers and no appearances are required. Note that this is an automatically generated message from the Clerk's Office and does not supersede any previous or subsequent orders from the Court. (jc,) [Transferred from New Jersey on 11/9/2021.] (Entered: 07/06/2021)
07/19/2021	10	BRIEF in Opposition filed by All Plaintiffs re 9 MOTION to Dismiss <i>pursuant to Fed.R.Civ.P. 12(b)(3) and to transfer venue</i> (WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 07/19/2021)
07/19/2021	11	Letter from Liza M. Walsh to Hon. Andre M. Espinoza, U.S.M.J.. (WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 07/19/2021)
07/19/2021	12	BRIEF in Opposition filed by All Plaintiffs re 9 MOTION to Dismiss <i>pursuant to Fed.R.Civ.P. 12(b)(3) and to transfer venue (Corrected)</i> (WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 07/19/2021)
07/21/2021	13	Letter from Midlige Richter to the Honorable Andre M. Espinosa, USMJ re response re 11 Letter. (RICHTER, JAMES) [Transferred from New Jersey on 11/9/2021.] (Entered: 07/21/2021)
07/26/2021	14	REPLY BRIEF to Opposition to Motion filed by NEXUS PHARMACEUTICALS, INC. re 9 MOTION to Dismiss <i>pursuant to Fed.R.Civ.P. 12(b)(3) and to transfer venue</i> (RICHTER, JAMES) [Transferred from New Jersey on 11/9/2021.] (Entered: 07/26/2021)
08/13/2021	15	ORDER Scheduling Initial R16 Conference for 9/8/2021 03:00 PM before Magistrate Judge Andre M. Espinosa. Signed by Magistrate Judge Andre M. Espinosa on 8/13/2021. (spc) [Transferred from New Jersey on 11/9/2021.] (Entered: 08/13/2021)
08/23/2021	16	Letter from Midlige Richter LLC re pro hac vice application on consent. (Attachments: # 1 Declaration of Imron Aly, # 2 Declaration of Joel Wallace, # 3 Declaration of James Richter, # 4 Text of Proposed Order)(RICHTER, JAMES) [Transferred from New Jersey on 11/9/2021.] (Entered: 08/23/2021)
08/30/2021	17	ORDER GRANTING PRO HAC VICE ADMISSION OF IMRON T. ALY, ESQ. AND JOEL M. WALLACE, ESQ.. Signed by Magistrate Judge Andre M. Espinosa on 8/30/2021. (ld,) [Transferred from New Jersey on 11/9/2021.] (Entered: 08/30/2021)
08/31/2021	18	Letter from Liza M. Walsh to the Hon. Andre M. Espinosa, U.S.M.J. re: Pro Hac Vice Application on Consent. (Attachments: # 1 Certification of Ha Kung Wong, # 2 Certification of Damien N. Dombrowski, # 3 Certification of Monica Chou, # 4 Certification of Liza M. Walsh, # 5 Text of Proposed Order)(WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 08/31/2021)
09/02/2021	19	TEXT ORDER -- The telephonic R16 conference scheduled in DE 15 Order will now take place on Friday September 10, 2021 at 10:00 AM with the same call in information. So Ordered by Magistrate Judge Andre M. Espinosa on 9/2/2021. (spc) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/02/2021)
09/07/2021	20	Joint Discovery Plan by All Plaintiffs.(WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/07/2021)

09/08/2021	<u>21</u>	Notice of Request by Pro Hac Vice Imron T. Aly to receive Notices of Electronic Filings. (Pro Hac Vice fee \$ 150 receipt number ANJDC-12781378.) (RICHTER, JAMES) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/08/2021)
09/08/2021	<u>22</u>	Notice of Request by Pro Hac Vice Joel M. Wallace to receive Notices of Electronic Filings. (Pro Hac Vice fee \$ 150 receipt number ANJDC-12781390.) (RICHTER, JAMES) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/08/2021)
09/08/2021	<u>23</u>	ORDER GRANTING PRO HAC VICE ADMISSION OF HA KUNG WONG, ESQ., DAMIEN N. DOMBROWSKI, ESQ., AND MONICA CHOU, ESQ.. Signed by Magistrate Judge Andre M. Espinosa on 9/8/2021. (ld,) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/08/2021)
09/08/2021		Pro Hac Vice counsel, IMRON T. ALY, ESQ. and JOEL M. WALLACE, ESQ., has been added to receive Notices of Electronic Filing. Pursuant to L.Civ.R. 101.1, only local counsel are entitled to sign and file papers, enter appearances and receive payments on judgments, decrees or orders. (ld,) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/08/2021)
09/09/2021	<u>24</u>	Notice of Request by Pro Hac Vice Ha Kung Wong to receive Notices of Electronic Filings. (Pro Hac Vice fee \$ 150 receipt number ANJDC-12784698.) (WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/09/2021)
09/09/2021	<u>25</u>	Notice of Request by Pro Hac Vice Damien N. Dombrowski to receive Notices of Electronic Filings. (Pro Hac Vice fee \$ 150 receipt number ANJDC-12784707.) (WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/09/2021)
09/09/2021	<u>26</u>	Notice of Request by Pro Hac Vice Monica Chou to receive Notices of Electronic Filings. (Pro Hac Vice fee \$ 150 receipt number ANJDC-12784712.) (WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/09/2021)
09/10/2021		Pro Hac Vice counsel, HA KUNG WONG, DAMIEN N. DOMBROWSKI and MONICA CHOU, have been added to receive Notices of Electronic Filing. Pursuant to L.Civ.R. 101.1, only local counsel are entitled to sign and file papers, enter appearances and receive payments on judgments, decrees or orders. (jc,) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/10/2021)
09/10/2021		Minute Entry for proceedings held before Magistrate Judge Andre M. Espinosa: Scheduling Conference held on 9/10/2021. Scheduling Order to be filed. (spc) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/13/2021)
09/17/2021	<u>27</u>	Joint Discovery Plan by All Plaintiffs.(WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/17/2021)
09/20/2021	<u>28</u>	ORDER that Plaintiffs' request for expedited discovery on Count I of the Complaint is DENIED; that Defendant's request for a stay of discovery is DENIED; that Plaintiffs' request that the Court order Defendant to provide Plaintiffs with notice of Defendant's launch of its generic product is DENIED; that the Court will hold a status conference on November 10, 2021, at 3:30 p.m.. Signed by Magistrate Judge Andre M. Espinosa on 9/20/2021. (ld,) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/21/2021)
09/24/2021	<u>29</u>	Letter from Liza M. Walsh Hon. Andre M. Espinosa, U.S.M.J.. (Attachments: # <u>1</u> Text of Proposed Order)(WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/24/2021)
09/30/2021	<u>30</u>	Letter from Liza M. Walsh to the Hon. Andre M. Espinosa, U.S.M.J. re: Proposed Discovery Confidentiality Order. (WALSH, LIZA) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/30/2021)

09/30/2021	31	Discovery Confidentiality Order. Signed by Magistrate Judge Andre M. Espinosa on 9/30/2021. (ld,) [Transferred from New Jersey on 11/9/2021.] (Entered: 09/30/2021)
10/05/2021	32	Letter from Midlige Richter LLC re pro hac vice application on consent. (Attachments: # 1 Declaration of Helen Ji, # 2 Declaration of James Richter, # 3 Text of Proposed Order) (RICHTER, JAMES) [Transferred from New Jersey on 11/9/2021.] (Entered: 10/05/2021)
10/07/2021	33	PRETRIAL SCHEDULING ORDER: Telephone Status Conference set for 11/10/2021 03:30 PM before Magistrate Judge Andre M. Espinosa. Amended Pleadings due by 4/1/2022. Joinder of Parties due by 4/1/2022.;etc. Signed by Magistrate Judge Andre M. Espinosa on 10/7/2021. (ld,) [Transferred from New Jersey on 11/9/2021.] (Entered: 10/07/2021)
11/02/2021	34	ORDER GRANTING PRO HAC VICE ADMISSION OF HELEN H. JI, ESQ.; that the application for the pro hac vice admission of Helen H. Ji, Esq. [ECF 32], is granted. Signed by Magistrate Judge Andre M. Espinosa on 11/2/2021. (ld,) [Transferred from New Jersey on 11/9/2021.] (Entered: 11/02/2021)
11/04/2021	35	MOTION to Dismiss <i>Count 1 of the Complaint</i> by NEXUS PHARMACEUTICALS, INC.. (Attachments: # 1 Brief, # 2 Declaration of James Richter with Exhibits, # 3 Text of Proposed Order)(RICHTER, JAMES) [Transferred from New Jersey on 11/9/2021.] (Entered: 11/04/2021)
11/05/2021		Set Deadlines as to 35 MOTION to Dismiss <i>Count 1 of the Complaint</i> . Motion set for 12/6/2021 before Judge Brian R. Martinotti. Unless otherwise directed by the Court, this motion will be decided on the papers and no appearances are required. Note that this is an automatically generated message from the Clerk's Office and does not supersede any previous or subsequent orders from the Court. (jc,) [Transferred from New Jersey on 11/9/2021.] (Entered: 11/05/2021)
11/05/2021	36	OPINION. Signed by Judge Brian R. Martinotti on 11/5/2021. (ld,) [Transferred from New Jersey on 11/9/2021.] (Entered: 11/05/2021)
11/05/2021	37	ORDER dismissing 35 Motion to Dismiss is MOOT; granting in part and denying in part 9 Motion to Dismiss; that this matter is TRANSFERRED to the Northern District of Illinois.. Signed by Judge Brian R. Martinotti on 11/5/2021. (ld,) [Transferred from New Jersey on 11/9/2021.] (Entered: 11/05/2021)
11/05/2021		***Civil Case Terminated. (ld,) [Transferred from New Jersey on 11/9/2021.] (Entered: 11/05/2021)
11/09/2021	38	RECEIVED from New Jersey; Case Number 2:21-cv-11198 (nsf) (Entered: 11/09/2021)
11/09/2021	39	MAILED Rule 83.15 Letter to all counsel of record. (nsf,) (Entered: 11/09/2021)
11/10/2021	40	EXECUTIVE COMMITTEE ORDER: Case reassigned to the Honorable Sharon Johnson Coleman for all further proceedings. Honorable Ronald A. Guzman no longer assigned to the case pursuant to 28 USC 294(b). Signed by Executive Committee on 11/10/2021.(daj,) (Entered: 11/10/2021)
11/10/2021	41	MINUTE entry before the Honorable Sharon Johnson Coleman: This case has been assigned to the calendar of Judge Sharon Johnson Coleman. Telephone status hearing is set for 12/3/2021 at 10:45 AM. The call-in number is (877)336-1829 and the access code is 5205245. The parties are directed to meet and discuss the status of the case. The parties are to file a joint status report in the format described on the court's website at www.ilnd.uscourts.gov at least 3 days prior to the status. Members of the public and media will be able to call in to listen to this hearing. Persons granted remote access to proceedings are reminded of the general prohibition against photographing, recording, and

		rebroadcasting of court proceedings. Violation of these prohibitions may result in sanctions, including removal of court issued media credentials, restricted entry to future hearings, denial of entry to future hearings, or any other sanctions deemed necessary by the Court. Mailed notice. (ym,) (Entered: 11/10/2021)
11/17/2021	42	ATTORNEY Appearance for Plaintiffs MELINTA THERAPEUTICS, LLC, Melinta Subsidiary Corp., Rempex Pharmaceuticals, Inc. by Brian Neil Anderson (Anderson, Brian) (Entered: 11/17/2021)
11/17/2021	43	MINUTE entry before the Honorable Sharon Johnson Coleman: Because this case was transferred to this Court on 11/9/2021, the Court strikes the pending motions from the District Court of New Jersey action, including the motions filed under that district's local rules. Mailed notice. (ym,) (Entered: 11/17/2021)
11/30/2021	44	STATUS Report by Melinta Subsidiary Corp., Melinta Therapeutics, LLC, Rempex Pharmaceuticals, Inc. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3)(Anderson, Brian) (Entered: 11/30/2021)
12/01/2021	45	MINUTE entry before the Honorable Sharon Johnson Coleman: Telephone status hearing set for 12/3/2021 is stricken. Mailed notice. (ym,) (Entered: 12/01/2021)
12/20/2021	46	MAIL RETURNED, for document # 41 sent to James S. Richter returned as undeliverable, return to sender. No new contact information received; therefore future mailings will not be sent until a new address is provided to the Clerk's Office using a Notification of Change of Address or Pro Se Appearance form (jg,) (Entered: 12/22/2021)
03/31/2022	47	MINUTE entry before the Honorable Sharon Johnson Coleman: Status hearing is set for 8/15/2022 at 9:30 AM and will proceed as an in-person hearing in courtroom 1241. Mailed notice. (ym,) (Entered: 03/31/2022)
04/27/2022	48	MAIL RETURNED, for document # 47 sent to James S. Richter returned as undeliverable, return to sender. No new contact information received; therefore future mailings will not be sent until a new address is provided to the Clerk's Office using a Notification of Change of Address or Pro Se Appearance form (jg,) (Entered: 04/28/2022)
08/10/2022	49	MINUTE entry before the Honorable Sharon Johnson Coleman: Status hearing set for 8/15/2022 is stricken. Mailed notice. (ym,) (Entered: 08/10/2022)
08/15/2022	50	EXECUTIVE COMMITTEE ORDER: Case reassigned to the Honorable John F. Kness for all further proceedings in accordance with the provisions of Local Rule 40.4 Related Case No. 21cv2636. Honorable Sharon Johnson Coleman no longer assigned to the case. Signed by Executive Committee on 8/15/2022. (jmk,) (Entered: 08/16/2022)
12/29/2022	51	ANNUAL REMINDER: Pursuant to Local Rule 3.2 (Notification of Affiliates) , any nongovernmental party, other than an individual or sole proprietorship, must file a statement identifying all its affiliates known to the party after diligent review or, if the party has identified no affiliates, then a statement reflecting that fact must be filed. An affiliate is defined as follows: any entity or individual owning, directly or indirectly (through ownership of one or more other entities), 5% or more of a party. The statement is to be electronically filed as a PDF in conjunction with entering the affiliates in CM/ECF as prompted. As a reminder to counsel, parties must supplement their statements of affiliates within thirty (30) days of any change in the information previously reported. This minute order is being issued to all counsel of record to remind counsel of their obligation to provide updated information as to additional affiliates if such updating is necessary. If counsel has any questions regarding this process, this LINK will provide additional information. Signed by the Executive Committee on 12/29/2022: Mailed notice. (tg,) (Entered: 12/30/2022)

12/28/2023	52	ANNUAL REMINDER: Pursuant to Local Rule 3.2 (Notification of Affiliates) , any nongovernmental party, other than an individual or sole proprietorship, must file a statement identifying all its affiliates known to the party after diligent review or, if the party has identified no affiliates, then a statement reflecting that fact must be filed. An affiliate is defined as follows: any entity or individual owning, directly or indirectly (through ownership of one or more other entities), 5% or more of a party. The statement is to be electronically filed as a PDF in conjunction with entering the affiliates in CM/ECF as prompted. As a reminder to counsel, parties must supplement their statements of affiliates within thirty (30) days of any change in the information previously reported. This minute order is being issued to all counsel of record to remind counsel of their obligation to provide updated information as to additional affiliates if such updating is necessary. If counsel has any questions regarding this process, this LINK will provide additional information. Signed by the Executive Committee on 12/28/2023: Mailed notice. (tg,) (Entered: 12/28/2023)
11/15/2024	53	MINUTE entry before the Honorable John F. Kness: This action is a companion case to Case No. 21-cv-02636, which was tried to the Court on a bench trial from June 6, 2023 to June 9, 2023. By separate orders in related case no. 21-cv-2636, the Court entered Findings of Fact and Conclusions of Law, and a final judgment in Plaintiffs' favor. In the time since the cases were consolidated on 12/07/2021, neither party has addressed this companion action, nor suggested or offered a suggestion that it remains open or different than 21-cv-2636 in any way. Accordingly, the Court will enter a final judgment in this companion case identical to the final judgment it entered in 21-cv-2636 and terminate this case. If the parties believe that the Court has misapprehended the status of this companion case in any way, they may file an appropriate motion. Mailed notice. (exr,) (Entered: 11/15/2024)
11/15/2024	54	ENTERED JUDGMENT. Mailed notice. (exr,) (Entered: 11/15/2024)
12/09/2024	55	NOTICE of appeal by Nexus pharmaceuticals, Inc. regarding orders 54 Filing fee \$ 605, receipt number AILNDC-22818244. Receipt number: n (Ji, Helen) (Entered: 12/09/2024)
12/10/2024	56	Entered in Error. (rc,) Modified on 12/10/2024 (rc,). (Entered: 12/10/2024)
12/10/2024	57	Entered in Error. Notified counsel. (rc,) Modified on 12/10/2024 (rc,). (Entered: 12/10/2024)
12/10/2024	58	NOTICE of Correction regarding transmitted short record to USCA 57 , notice of appeal due letter 56 . (rc,) (Entered: 12/10/2024)
12/10/2024	59	TRANSMITTED to the Federal the short record on notice of appeal 55 . Notified counsel. (rc,) (Entered: 12/10/2024)
12/13/2024	60	ACKNOWLEDGMENT of receipt of short record on appeal regarding notice of appeal 55 ; USCA for the Federal Circuit Docket No. 2025-1282 (jxm,) (Entered: 12/16/2024)

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**IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS**

MELINTA THERAPEUTICS, LLC,
MELINTA SUBSIDIARY CORP., and
REMPEX PHARMACEUTICALS, INC.,

Plaintiffs,

V.

NEXUS PHARMACEUTICALS, INC.,

Defendant.

C.A. No. 1:21-cv-02636

Judge John F. Kness

Magistrate Judge Maria Valdez

PLAINTIFFS' OPENING POST-TRIAL BRIEF

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reconstituted solution, prior to further dilution for administration. (FOF, ¶¶ 53-55.) That is how pH is defined for the prior art intravenous minocycline composition, the new Minocin® composition, and the composition of Defendant’s ANDA product. (FOF, ¶ 56.) The pH of the further diluted admixture is not a formal drug specification for any of those products. (*Id.*) Defendant’s expert Dr. Klibanov admitted that the “composition” of Minocin® and Defendant’s ANDA product is the reconstituted solution prior to further dilution, as identified in the Description section of the labels for those products. (FOF, ¶ 57.) The components listed in Defendant’s ANDA for its “composition” are the same ingredients that are recited in the patent claims (*e.g.*, aqueous solution of minocycline hydrochloride, magnesium sulfate heptahydrate, and sodium hydroxide as a base), but that list does *not* include the diluents used to administer the composition. (FOF, ¶ 58.)

Contrary to Dr. Klibanov’s contention, there is no inconsistency in how the word “composition” is used in the ’802 patent. (Tr. at 523:21-524:14.) In claims 1 and 18, the term “composition” refers to the reconstituted solution in the vial, and claim 18 further recites the “total volume” of the composition as “administered,” *i.e.*, total volume after further dilution for injection. (FOF, ¶ 59.)

2. Defendant’s Proposed Construction

Defendant’s proposed construction of “composition” is the further diluted solution for administration. (Tr. at 522:3-20, 554:17-20, 586:25-587:24, 671:13-672:5; DDX-1036.) Defendant’s experts did not point to any support in the patent specification or any prior art references supporting their interpretation of the claims or suggesting that a POSA would understand the pH to be defined with respect to the further diluted admixture.

Moreover, Defendant’s construction is mistaken and makes no sense. For example, Defendant argues non-infringement on the basis that (1) when further diluted for administration,

Defendant's ANDA product includes a diluent, and (2) the "consists/consisting of" language in claim 1 of the '802 patent legally excludes such a diluent from the "composition" (as Defendant construes the term). (Tr. at 215:13-17, 520:14-522:2, 522:21-523:16, 524:15-525:10, 556:7-16; DDX-2044-2046.)¹ But it is undisputed that the reconstituted solution of minocycline is never directly administered, and it is always necessary to further dilute the solution for intravenous administration. (FOF, ¶ 60.) Defendant is arguing on the one hand that "composition" is the further diluted admixture for administration, but on the other hand the "consists/consisting of" language excludes any diluents from the "composition." Under Defendant's proposed construction there could never be *any* intravenous "composition" of minocycline that could infringe, including the minocycline compositions disclosed in the patent specification (which includes Minocin®). This confirms that Defendant's proposed construction of "composition" cannot be correct. (Tr. at 555:1-5, 556:7-16.) *See, e.g., Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1255 (Fed. Cir. 2010) (interpretation that renders claims nonsensical cannot be correct); *Vitronics Corp. v. Conceptiontronic, Inc.*, 90 F.3d 1576, 1583-84 (Fed. Cir. 1996) (interpretation that excludes from claims a preferred embodiment described in the specification is "rarely, if ever, correct"); *Phillips*, 415 F.3d at 1316 ("The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.").

As discussed below, Defendant infringes, and the asserted claims are valid under either party's proposed construction of "composition."

¹ Dr. Klivanov also stated that Defendant would not infringe if the Court finds that the term "composition" refers to the reconstituted solution, but he did not provide any further explanation, evidence, or argument to support that assertion. (Tr. 523:17-20.)

knowledge how to administer formulations at very small volumes; how to adjust volume, administration rate, and dosing frequency as needed to administer a therapeutically effective amount; and not to go so low as to affect efficacy or safety. (FOF, ¶ 233.)

July 12, 2023

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CERTIFICATE OF SERVICE

The undersigned certifies that on July 12, 2023, the foregoing document was served on counsel of record by operation of the Court's CM/ECF system.

/s/ Mark Deming

**IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS**

MELINTA THERAPEUTICS, LLC,)	
MELINTA SUBSIDIARY CORP., and)	
REMPEX PHARMACEUTICALS, INC.,)	
)	
Plaintiffs,)	C.A. No. 1:21-cv-02636
)	
v.)	Judge John F. Kness
)	
NEXUS PHARMACEUTICALS, INC.,)	Magistrate Judge Maria Valdez
)	
Defendants.)	
)	

DEFENDANT NEXUS PHARMACEUTICALS, INC.'S POST TRIAL BRIEF

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Plaintiffs’ two patents treat no new bacterial infections, change no side effects, and simply followed the prior art instructions to add magnesium to old minocycline formulations. Yet Plaintiffs seek to use these weak patents to block competition. At trial, Plaintiffs made many conclusory arguments through their experts, but without any documented support. Plaintiffs’ expert Dr. Bruce Friedman asserted the changed formulation “changed the game” but beyond say-so pointed to no publications supporting that opinion—not even any of his own 300+ publications. Similarly, for the central ’802 patent claim term “reduced injection site hemolysis,” Dr. Friedman repeatedly offered his unsupported opinion that the new formulation improved tolerability issues over the old formulation—even though the FDA expressly reached the exact opposite conclusion. Meanwhile, Plaintiffs’ expert Dr. Tina deVries argued that no one could rely on doxycycline formulations in the prior art just because it is not the same drug as minocycline, but conceded the two drugs are identical on the “bottom half” precisely where magnesium interacts. For the main ’105 patent claim term, she never did the “very easy” osmolality test.

Judgment should be entered in favor of Nexus because (1) Plaintiffs failed to prove infringement—direct or indirect; (2) Nexus proved the claimed inventions followed the prior art roadmap and are therefore obvious; and (3) Nexus proved the patent specifications do not show enough to warrant the claim scope, so the claims are invalid under Section 112 of the Patent Act.

Infringement: Plaintiffs did not prove infringement with appropriate testing data, and therefore assumed key features existed, which is not sufficient to meet their burden. For the '802 patent, Plaintiffs had to show reduced injection site hemolysis, but none of the experiments Plaintiffs did (including on rabbit red blood cells) proved any clinical difference in the real-life conditions in which Nexus's product will be used. The only actual vein tests they did—three using rabbit ears—all failed, confirming current Minocin IV venous tolerance was no different than old

Minocin IV. The FDA told Plaintiffs they needed to do clinical trials (actual head-to-head testing in humans) to demonstrate improved tolerability, which Plaintiffs chose not to do. For the '105 patent, Plaintiffs had to show Nexus's product osmolality is below 500 mOsmol/kg, but failed to do so either for the reconstituted vial (using Plaintiffs' claim construction) or the diluted bag (using Nexus's construction). Plaintiffs used the wrong volume for the vial osmolality testing data and ended up proving non-infringement, and never bothered to test any diluted bag product osmolality.

Even if Plaintiffs had shown direct infringement, they still had to show that Nexus knowingly aids and abets infringement by others, through the indirect infringement doctrines of inducement and contributory infringement. But Nexus is indifferent to the patents' injection site hemolysis or osmolality, and instead seeks to sell minocycline to treat bacterial infections. Plaintiffs pointed to Nexus's general statements that osmolality "should be isotonic"—without showing any numbers that the claims require—and statements that magnesium can be a "hemolysis reducer"—without addressing proof of "injection site" hemolysis. Neither of these claimed features are on Nexus's label, as there is no mention of osmolality (much less the required less than 500 mOsmol/kg) nor hemolysis (much less reduced injection site hemolysis).

Obviousness: Nexus showed through Dr. Alexander Klibanov that the claimed formulations were obvious because they followed a roadmap published in the prior art. The old Minocin IV product taught nearly everything in the claims except for magnesium. CN'268 taught adding magnesium to unlock benefits including solubility, stability, increased pH, and improved tolerability—using the closely-related doxycycline drug. And Gibbs used doxycycline and minocycline interchangeably when discussing formulations, and used magnesium formulations with molar ratios up to 8:1, overlapping with the asserted claims. For pH, the old and current Minocin IV products have the same or nearly the same pH ranges, especially for the administered

formulation where pH could be relevant. For volume, Plaintiffs admitted to FDA that people were already using volumes less than 500 mL with the old Minocin IV product. And Plaintiffs' experts posited that injection site hemolysis and osmolality are inherent properties, so they add nothing to the claims for an invalidity analysis. Plaintiffs can't have it both ways: either there is no direct infringement since there is not enough proof, or else the key "osmolality" and "injection site hemolysis" limitations can be assumed, making the claims invalid. Plaintiffs turned to secondary considerations, hoping to undo clear and convincing obviousness, but again without actual evidence. No amount of secondary considerations changes the strong obviousness anyway.

Patent defects: The claims were poorly drafted and tried to cover too much. Nexus showed that claims to broad ranges like pH "4 to 7," osmolality for the entire range "less than about 500," and volume for the full "less than 500" were not operable, and therefore invalid as lacking enablement and written description. Nexus also showed through Dr. Henry Chambers that "reduced injection site hemolysis" is undefined and invalid as indefinite.

I. BACKGROUND

A. The Asserted Claims

Plaintiffs assert claim 27 from U.S. Patent 9,278,105 and claims 1, 7, and 18 from U.S. Patent 9,084,802. These are all method claims, requiring users to administer minocycline IV containing magnesium and to achieve certain claimed features. Claim 27 of the '105 patent requires an "osmolality less than about 500 mOsmol/kg." Claim 1 of the '802 patent—and therefore also claims 7 and 18 since they are dependent on claim 1—require "reduced injection site hemolysis" compared to "a composition that does not include magnesium."

B. The Minocin IV Products

Minocin IV was commercially available in the 1970s. *See* DTX-0072 at 4. It was briefly taken off the market in 2005 and returned in 2009, before the priority date of the asserted patents.

Tr. 705:8-10, 707:11-13 (Friedman). Dr. Friedman admitted that old Minocin IV was not removed due to safety or efficacy. Tr. 759:20-760:5. Shortly after the old Minocin IV product returned to market, Plaintiff Rempex acquired the New Drug Application for the magnesium-minocycline product and explained to FDA that the “new” formulation “is the same as that of the current formulation, except for the addition of magnesium sulfate (USP), and NaOH (USP) for pH adjustment” and that it would be used “for the same indications using the same dosage regimens” as the old formulation, with “no change in infusion time.” DTX-0072_0003, 0007. Plaintiffs sought to change the label to show the changed formulation “improved tolerability,” but FDA refused unless Plaintiffs undertook clinical trials, which they never did. *Id.* at 0006. Tr. 601:3-12 (Chambers). Plaintiffs instead “acquired” the old Minocin IV formulation and replaced it with their magnesium formulation. *Id.* The two never competed side-by-side.

C. Nexus’s ANDA Minocycline Product

Nexus filed an Abbreviated New Drug Application (“ANDA”), to develop a generic minocycline IV product, certifying that Plaintiffs’ patents are not infringed and invalid. Nexus referenced the only available minocycline IV product, the magnesium-minocycline Minocin IV. The FDA filing resulted in this litigation, and the resolution on these patent issues will decide whether Nexus can now launch its generic minocycline IV product.

II. PLAINTIFFS’ CLAIM CONSTRUCTIONS WERE IMPROPERLY RAISED AT TRIAL AND WRONG AS A MATTER OF LAW

In patent cases, claim construction is of such critical importance that a separate phase of litigation is devoted to it. The Supreme Court confirmed that claim construction is a question of law, and applying the construed claims for infringement is a question of fact. *Markman v. Westview*, 517 U.S. 370, 384-385 (1996). Over the years, so-called “Markman” hearings have been universally held to construe terms well in advance of trial.

Consistent with Local Patent Rules 4.1-4.3, the Court entered a Scheduling Order that provided a schedule for exchanging, briefing, and resolving claim construction issues before exchanging any expert reports. D.I. 36. Yet in February 2022, when it came time to raise any issues—and even after seeing Nexus’s contentions—Plaintiffs reported that no claim terms required construction. Only Nexus raised any issue at all, confirming with Plaintiffs that “consists of” is an understood legal term, and that indefiniteness invalidity issues under 35 U.S.C. § 112 would be dealt with at trial. *See* Ex. A, 2/21/22 Email. The parties thus informed the Court in April 2022 that claim construction would be unnecessary. D.I. 70.

At trial, however, Plaintiffs asked the Court to construe several claims, adding to and changing clear claim terms. But the time and place for claim construction had already passed, so Nexus objected. Plaintiffs assert that their proposed constructions are in their experts’ reports, but that entirely misses the point: expert reports were issued well after the Court’s Order and prescribed process for claim construction. Plaintiffs waived any claim construction arguments in violation of the Local Patent Rules and this Court’s Order.

Even if claim construction is entertained at this late stage, Plaintiffs still did not justify any of their proposed claim constructions. Plaintiffs point to articles and expert testimony, when the focus is supposed to be on the claim itself. “It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2012) (internal quotation marks omitted). “The name of the game is the claim.” *In re Hiniker Co.*, 150 F.3d 1362, 1369 (Fed. Cir. 1998).

The five claim terms at issue here—“administering,” “composition,” “consists of/consisting of,” “subject,” and “does not include magnesium”—are readily understood words. Any further construction is unnecessary because the “plain and ordinary meaning” is already clear

and should not be changed to suit Plaintiffs’ litigation-oriented redefinitions. *See, e.g., Philips*, 415 F.3d at 1312-13. Plaintiffs’ efforts violate the clear rules that “[w]e do not read limitations from the specification into the claims; we do not redefine words.” *Thorner v. Sony Computer Entm’t Am., LLC*, 669 F.3d 1362, 1366 (Fed. Cir. 2012).

A. “Administering” Means Administering, Not “Dilute And Then Administer”

All four asserted claims use the word “administering,” and the word reflects one step: giving or providing minocycline into the subject’s blood stream. PTX 1, claim 1; PTX 2, claim 1. Plaintiffs are trying to re-draft their claims by adding language to make “administering” involve two steps, first diluting the reconstituted formulation and then administering the diluted product. Tr. 720:4-721:13. Plaintiffs ignore the starting point of any claim construction: the words of the claims themselves. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The claims state “administering...a composition” as claimed and not adding diluents.

Another source for claim construction can be the patent specification. *Vitronics*, 90 F.3d at 1582. Still, the specification “cannot be used to narrow a claim term to deviate from the plain and ordinary meaning unless the inventor acted as his own lexicographer or intentionally disclaimed claim scope.” *Aventis Pharms., Inc. v. Amino Chems, Ltd.*, 715 F.3d 1363, 1373 (Fed. Cir. 2013). Here, the specification nowhere defines “administration,” nor requires dilution as part of administration. *See Thorner*, 669 F.3d at 1365 (“patentee must ‘clearly express intent’ to redefine a term” to deviate from plain and ordinary meaning). Example 13 itemizes fourteen different formulations, the first eight of which are “for intravenous administration” without mentioning dilution. PTX 1 at 38:1-39:55. The specification separately refers to “admixture” and “patients,” but neither of those words is in the claims. *Id.* at 13:47-56.

The way that the patent claims were written may very well end up causing Plaintiffs issues for patent infringement and invalidity. But that is a separate and independent inquiry. Claims must

be construed “without the objective of capturing or excluding the accused device.” *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1324 (Fed. Cir. 2009).

B. The “Composition” Is What is Administered.

Because the claim uses “composition” to describe what is administered to treat a bacterial infection, the plain and ordinary meaning of “composition” is whatever is administered. The language of the asserted claims themselves makes clear that the claimed “method of treating a bacterial infection” is in part achieved by “administering a therapeutically effective amount of a composition.” *See, e.g.*, PTX 1 at claim 1. The specification shows that “composition” refers to what is administered and can take many forms, so the rest of the claim language defines the product to be administered. The specification describes “administering the pharmaceutical composition...to the subject via an intravenous route of administration” (*id.* at 6:26-30; *see also* 6:31-36), and further refers to administering “less than 200 mL of the composition” and “administering the composition in less than 60 minutes.” *Id.* at 6:37-41.

Plaintiffs argue “composition” does not mean what is administered, but instead is an intermediate reconstituted product before dilution. The specification does not require the composition to be the reconstituted product since it says the opposite: “some compositions include solutions resulting from diluting those reconstituted solutions with pharmaceutically acceptable diluents for use in intravenous bags.” PTX 1 at 12:31-34. The specification gives no special definition, so there is no need to deviate from the ordinary meaning. The Court cannot rewrite the claims. *See K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1364-65 (Fed. Cir. 1999) (“Courts do not rewrite claims; instead, we give effect to the terms chosen by the patentee.”).

C. Patentee’s Use of “Consists of” And “Consisting of” In The ’802 Patent Limits The Asserted Claims To Administer Only The Listed Ingredients.

The ’802 patent claims use “consists of” three times in a row, to limit and further limit the

claimed method to administering a formulation with only the listed ingredients. “Consists of” is “understood to exclude any elements, steps, or ingredients not specified in the claim.” *AFG Indus., Inc. v. Cardinal IG Co.*, 239 F.3d 1239, 1245 (Fed. Cir. 2001); *see also* Tr. 215:13-17 (deVries).

As seen below, claim 1 of the ’802 patent, and therefore dependent claims 7 and 18 as well, use the closed-ended term three times to continually narrow the claim scope:

1. A method of treating a bacterial infection in a subject, wherein the method **consists of**: administering a therapeutically effective amount of a **composition** to a subject in need thereof via an intravenous route of administration, wherein **the composition consists of an aqueous solution consisting of minocycline or a salt thereof, a salt that comprises a magnesium cation, and a base,...**

PTX 1 at 40:43-50 (emphases and coloring added). The ’802 patent asserted claims, therefore, limit the method to only administering a therapeutically effective amount of a **composition**, and the composition is only **an aqueous solution** that itself contains only the three components identified above in green (minocycline, magnesium cation, and base). No other method steps are permitted and no other components of the composition are allowed.

Plaintiffs focus on extrinsic observations about how the commercial product is actually used, by adding a diluent, but claims are construed according to intrinsic evidence based on what the patent says. *Myco Indus., Inc. v. BlephEx, LLC*, 955 F. 3d 1, 15 (Fed. Cir. 2020) (“claim construction...focuses on the recited limitations of the *claims*, not on the features of a commercial embodiment of the invention.” (emphasis in original)). Plaintiffs’ approach would turn claim construction upside down: first looking at what people do in practice, and then construing the claim. The claims do not say the composition contains a diluent. “Where, as here, the claim is susceptible to only one reasonable construction...[the Court] must construe the claims based on the patentee’s version of the claim as he himself drafted it.” *Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) (*quoting Process Control Corp. v. Hydrex Corp.*, 190 F.3d 1350, 1357 (Fed. Cir. 1999)). In *Chef America*, the claims said to heat dough “to” a

temperature, rather than “at” a temperature. *Id.* at 1373-74. Even though everyone realized that doing so literally would mean “burn[ing] to a crisp” the dough, the Federal Circuit confirmed that “courts may not redraft claims” and required the claim word to stand rather than change it to how “patentees wish they had written it.” *Id.* The same must be true here.

D. Plaintiffs Improperly Redefine “Subject” To Be Limited To “Human.”

For all four asserted claims, the patentee chose to use the broader catch-all term “subject” instead of the narrow example of “human.” PTX 1, claim 1; PTX 2, claim 1. That choice must be enforced. The claims define the boundary of the alleged invention, and the claim scope is not limited to any individual embodiment, especially not a commercial embodiment that did not exist until much later in time. *Myco*, 955 F. 3d at 15.

The legal question for claim construction is whether the claim term “subject” is limited to only “human,” and there is no basis for that conclusion in the context of the patent claims. The plain language of the claims confirms that “subject” means any animal. The only restriction is to treat the animal for “a bacterial infection.” So while “subject” includes humans, the term is not limited because the patentee used “subject” instead of “human.” The patent uses “subject” throughout the specification, and it uses “human” only in Example 12, (PTX 1 at 6:26-30, 37:6-67), which shows the patentee knew how to use the word “human” when desired. The specification otherwise provides tests in different animal cell models, like rabbit red blood cells, as shown in each of Figures 1-5 in the ’802 patent. “Subject” therefore means any animal.

E. The Term “Does Not Include Magnesium” Should Be Given Its Plain And Ordinary Meaning.

For the three asserted claims of the ’802 patent, the term “a composition that does not include magnesium” should be construed to mean just that. Plaintiffs want to change the clear language of “does not include *magnesium*” to “does not include magnesium *or another metal*

cation.” No intrinsic or extrinsic evidence permits such a modification to the claim term.

The claim itself and the specification are clear about the word “magnesium.” First, the claim term itself refers to magnesium alone and no other metal, and it does so in two places: one to reference the claimed formulation that has “a magnesium cation” and then the comparator formulation that “does not include magnesium.” PTX 1 at 40:48-50, 55-57. Second, the specification explains that metal cations include “common” examples like “iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium.” PTX 1 at 10:4-9. This separate itemization of different metal cations shows that if the patentee wanted to do so, it could have written the claim to list any or all of these metals or could have even just said “does not include magnesium or another metal cation.” But that is not what happened.

III. PLAINTIFFS FAILED TO MEET THEIR BURDEN TO SHOW INFRINGEMENT

Plaintiffs sued Nexus for indirect infringement, so Plaintiffs have to prove both (a) direct infringement by third parties and (b) indirect infringement liability by proving either inducement or contributory infringement. Nexus renews its Motion for Summary Judgment (D.I. 194, 198), and its Motion Pursuant to Rule 52(c) (455:14-456:21).

A. Plaintiffs Bear The Burden to Prove Direct And Indirect Infringement

On direct infringement, Plaintiffs bear the burden of persuasion for “every limitation” by a preponderance of evidence. *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1535 (Fed. Cir. 1991). Plaintiffs must show every limitation is *literally* present, as plaintiffs did not raise any issue at trial under the “doctrine of equivalents.” Without any direct infringement, there can be no indirect infringement; “direct infringement [] is a prerequisite for indirect infringement.” *Takeda Pharms. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 634 (Fed. Cir. 2015). Even if there had been proof physicians directly infringe, Plaintiffs failed to show that Nexus should be liable.

1. Induced infringement

For induced infringement, Plaintiffs had to prove Nexus actively encouraged others to infringe. “The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient for inducement.” *Takeda*, 785 F.3d at 631. The Supreme Court confirmed that “induced infringement under § 271(b) requires knowledge that the induced acts constitute patent infringement.” *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 766 (2011). Plaintiffs must further show “specific intent and action to induce infringement must be proven.” *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363- 64 (Fed. Cir. 2003). “It is not enough to simply intend to induce the infringing acts” as Plaintiffs must prove inducing “actual infringement.” *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1331-32 (Fed. Cir. 2010).

Here, because Nexus’s ANDA label is the “only information or instruction” that Nexus provides, (Tr. 246:23-247:6 (deVries)), Plaintiffs had to show inducement by proving Nexus “has or will promote or encourage doctors to infringe the [] method patent,” with statements on the label telling users to infringe. *Warner-Lambert*, 316 F.3d at 1364; *see also HZNP Medicines LLC v. Actavis Laboratories UT, Inc.*, 940 F.3d 680, 699 (Fed. Cir. 2019).

2. Contributory infringement

For contributory infringement, Plaintiffs must show that Nexus will sell a product “for use in practicing a patented process” with knowledge the product was “made or especially adapted for use in an infringement” and without “substantial noninfringing use.” 35 U.S.C. § 271(c). Contributory infringement, like inducement, still requires proof of actual direct infringement, because direct infringement cannot be assumed on “mere inferences.” *DSU Medical Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1304-1305 (Fed. Cir. 2006) (affirming non-infringement for needle shield sold in open configuration without evidence it was ever closed). Knowledge of infringement means not just knowing about “the patent and of the relevant acts,” but also that the product use

“was both patented *and infringing*.” *Fujitsu*, 620 F.3d at 1330 (emphasis added). “Like induced infringement, contributory infringement requires knowledge of the patent in suit and knowledge of patent infringement.” *Commil USA, LLC v. Cisco Sys., Inc.*, 575 U.S. 632, 639 (2015).

B. Plaintiffs Did Not Prove Infringement: No Data For Direct Infringement and No Knowledge/Intent For Indirect Infringement

Plaintiffs did not show direct infringement because at least one claim requirement is missing or not proven. As discussed below, Plaintiffs failed to show Nexus’s product has an “osmolality of less than about 500 mOsmol/kg” as required by the ’105 patent and that “injection site hemolysis” will be reduced as required by the ’802 patent. While Nexus and Plaintiffs share the same formulation, it is legal error to compare the two formulations to each other and assume both meet the claim terms. *See Zenith Labs. v. Bristol-Myers Squibb*, 19 F.3d 1418, 1423 (Fed. Cir. 1994) (“As we have repeatedly said, it is error for a court to compare in its infringement analysis the accused product or process with the patentee's commercial embodiment or other version of the product or process; the only proper comparison is with the claims of the patent.”).

1. Osmolality (claim 27 of the ’105 Patent)

Under either parties’ construction, Plaintiffs failed to prove direct or indirect infringement. One issue raised by Plaintiffs’ belated claim construction dispute is whether “administering a composition” means the solution in a vial (reconstituted) or the solution in an IV bag (diluted). Plaintiffs failed under either construction.

a) Under Plaintiffs’ vial-focused construction of “administering a composition,” Plaintiffs failed to show direct or indirect infringement for osmolality.

Plaintiffs say claim 27 of the ’105 patent is met if the reconstituted solution in the vial—when 5 mL water is added—has an osmolality of less than 500 mOsmol/kg. Plaintiffs’ own evidence disproves direct infringement.

(1) No osmolality direct infringement (vial construction)

All minocycline IV products (old Minocin, new Minocin, and Nexus’s product) instruct reconstituting with 5 mL of water. DTX-112_0013, DTX-110_0010, PTX 42 at NEXUS-MIN-0001213. Plaintiffs provided no osmolality measurement, however, for any product reconstituted with 5 mL of water. Plaintiffs’ expert Dr. deVries agreed the osmolality test is a “very easy” one that takes “minutes.” Tr. 254:15-24. But she did not do any tests. Tr. 255:5-7. Instead, Dr. deVries relied on Plaintiffs’ development records (before commercial products were ever made). Tr. 262:2-9. Dr. deVries insisted the data she presented related to vials with 5 mL water added, Tr. 236:21-237:22, 239:13-239:25, but admitted on cross examination that the testing data actually used 10 mL water—as expressly stated on the document. Tr. 268:8-12. Once confronted with that material difference between 10 mL in the tests and 5mL in the actual Nexus product, Dr. deVries testified that a “first guess approximation would be that the osmolality would double.” Tr. 307:20-308:4. Applying that doubling approximation, however, means that the data she reported using 10 mL reconstitution (ranging from 286-302 mOsmol/kg, *see* PDX-2039, citing PTX-197) would really be higher if 5 mL had been used (ranging from 572-604 mOsmol/kg). In other words, Dr. deVries’s own data and testimony showed that the vial osmolality test results would be well **over** the required 500 mOsmol/kg threshold required by claim 27 of the ’105 patent.

(2) No osmolality indirect infringement (vial construction)

Because Plaintiffs failed to prove direct infringement, Nexus cannot be liable for indirect infringement, as a matter of law. *Takeda*, 785 F.3d at 634. Regardless, Plaintiffs failed to prove either contributory or induced infringement.

As to contributory infringement, still under Plaintiffs’ vial-based claim construction, Plaintiffs offered no evidence that Nexus knew the osmolality of the solution in a reconstituted

vial, much less that Nexus knew it would infringe the patent. *See, e.g., Fujitsu*, 620 F.3d at 1330. To the contrary, the only evidence that Plaintiffs offered at trial was Nexus’s deposition testimony by Dr. Suprita Tawde who testified that “once it is diluted” the formulation “should be isotonic,” but (1) that related only to the diluted formulation and not the reconstituted vial, and (2) she did not know any numeric value because any particular osmolality “is not a requirement.” Tawde Dep. 73:23-74:9. Moreover, Plaintiffs failed to show “no substantial non-infringing uses” as required by statute, *see* 35 U.S.C. § 271(c), especially since Plaintiffs’ own data proved non-infringing uses with osmolality over 500 mOsmol/kg.

Finally, as to induced infringement, it remains undisputed that Nexus’s label does not even mention osmolality—neither for the reconstituted vial nor the diluted and administered IV bag. Nexus’s label is silent on osmolality. Nexus’s label only has one instruction: to treat bacterial infections. PTX042, at 1. Nexus’s label is and will be indifferent as to what osmolality is used at any stage, whether for reconstituting, diluting, or administering. Because Nexus’s label does not mention osmolality, Nexus cannot induce infringement. *Takeda*, 785 F.3d at 631 (“label must encourage, recommend, or promote infringement”).

b) Under Nexus’s construction focused on the administered composition, Plaintiffs also failed to show infringement of the osmolality limitation.

Under Nexus’s construction, the 500 mOsmol/kg requirement applies to the diluted product that is administered. Plaintiffs provided no data at all about the osmolality of diluted formulations.

(1) No osmolality direct infringement (IV bag construction)

Instead of any test or even calculation, Plaintiffs’ expert Dr. Friedman relied on the reported osmolarities for certain off-the-shelf diluent options where the “milliosmols are under 500.” Tr. 142:9-18. The problem with this analysis, however, is that Dr. Friedman looked only at

the standalone IV bag osmolality *before* any vial contents were added. He did not present the osmolality of an IV bag *after* adding the reconstituted vial contents, including the minocycline, magnesium, and base. He only looked at each separately. Tr. 139:21-140:9. Since osmolality is a measurement of particles in solution, Dr. Friedman’s analysis of the IV bag by itself, without all of the particles combined together was necessarily incomplete. While he kept repeating that “you could calculate it,” Dr. Friedman never presented an osmolality calculation. Tr. 137:7-10; 435:7-19. Same for Dr. deVries. Tr. 255:16-256:6.

Plaintiffs thus resorted to Nexus’s *invalidity* position, articulated by medical expert Dr. Chambers, that it would be consistent with the prior art standard of care to administer IV formulations having osmolalities less than 500 mOsmol/kg. But the standard of care shows that a certain threshold would have been obvious to use, not proof that a formulation actually uses less than 500 mOsmol/kg. If one can assume direct infringement based on the standard of care alone, then that only further strengthens Nexus’s invalidity position, since the 500 mOsmol/kg was obviously nothing new or special. This is the “either-or” path presented during opening statements: either Plaintiffs failed to prove direct infringement because they showed no osmolality testing, or direct infringement can be assumed based on the standard of care, in which case the claimed osmolality is an inherent property and the asserted claim is invalid as obvious.

(2) No osmolality indirect infringement (IV bag construction)

Beyond direct infringement, however, Plaintiffs still failed to prove indirect infringement under the IV bag-based claim construction, either for contributory or inducement. As to contributory infringement, Plaintiffs never proved knowledge of infringement. Dr. Tawde’s testimony that the diluted and administered formulation “should be isotonic” is not the same as knowledge of infringement, because Plaintiffs never showed that Nexus measured or confirmed

the osmolality level to see if it was less than 500 mOsmol/kg—the specific threshold required by the claim. Plaintiffs also failed to show another key requirement for contributory infringement, that there are “no substantial non-infringing uses.” *See* 35 U.S.C. § 271(c). To the contrary, even if Dr. Friedman’s reliance on only the IV bag alone (without any drug) would have been sufficient, then Dr. Chambers explained that at least one listed diluent option permitted by the label would exceed the 500 mOsmol/kg cutoff. Tr. 654:21-25, 681:9-22.

There is no induced infringement either, for the same reasons discussed above. Nexus’s label is silent on osmolality, or how to measure it, or any threshold. For inducement, Plaintiffs must show Nexus has a specific intent to actively encourage or instruct practicing the claimed method. *See Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1324 (Fed. Cir. 2012) (holding that without FDA approval, brand’s “label cannot instruct (and the ANDA proposed label cannot induce infringement of)” asserted claims). Whether for the vial or the diluted IV bag, Nexus’s label does not mention and is indifferent to the claimed osmolality level. Nexus will sell minocycline to treat bacterial infections, and that is not infringement because Plaintiffs did not invent treating bacterial infections with minocycline. *Id.* at 1326 (affirming non-infringement where “there is no valid patent on the use of the drug for that purpose alone”). To the contrary, and unrelated to the label, Dr. Friedman explained that pharmacists independently do their own osmolality assessment, meaning Nexus will not cause any potential infringement that pharmacists do on their own. Tr. 137:10-23.

2. Reduced Injection Site Hemolysis (claims 1, 7, and 18 of the ’802 Patent)

All three asserted claims of the ’802 patent require “injection site hemolysis” “reduced” “relative to” a formulation “that does not include magnesium.” Plaintiffs failed to prove direct infringement because they never showed any instance of “injection site hemolysis” with any

formulation, much less reduced injection site hemolysis with Nexus's formulation.

a) Plaintiffs failed to show direct infringement

First, just as the FDA also concluded, Plaintiffs' experiments are not enough to justify any claimed improvement in tolerance in actual human use. The patent specification describes rabbit red blood cell tests, where the blood cells in a lab setting were exposed to minocycline. Based on those tests, which show reduced *hemolysis* under some lab-scale experimental conditions, Dr. Friedman attempted to conclude that Nexus's product will reduce *injection site hemolysis* in actual patients. But Nexus's minocycline IV product will not be administered to petri dishes. Plaintiffs therefore had to show reduced hemolysis in humans to show infringement, and failed to do so. The best Plaintiffs could tell the FDA, with all their "preclinical studies in vitro and in vivo" in hand, was that the minocycline-magnesium formulation "has the *potential* to reduce infusion site intolerability." PTX 88, at 3. In the same document, to test whether the potential could be demonstrated, Plaintiffs proposed a Phase 1 clinical trial for "infusion site phlebitis." *Id.* FDA stated even more would be required, with "two superiority trials...designed to show better tolerance, less phlebitis." *Id.* at 4. But rather than do the tests, Plaintiffs "acquired" the existing NDA, so they would not have to compete with it on the market, and "the clinical trial...to support label claims for improved tolerability was considered no longer necessary and was not conducted." DTX-0072_0006; Tr. 864:6-9 (deVries). In fact, the only tests that Plaintiffs actually did in any IV setting to evaluate venous tolerance used rabbit ear veins, and Dr. deVries admitted three tests in a row showed no difference between formulations with and without magnesium—even when very high drug doses were used. 864:17-870:23; DTX-41_0005-8.

Second, none of the tests that Plaintiffs rely upon show reduced injection site hemolysis "relative to...a composition that does not include magnesium." Plaintiffs accuse Nexus's product of infringing this claim term, but they did not compare Nexus's product to any other (or even

compare Plaintiffs' product to any other). Dr. deVries confirmed that her opinion required showing reduced injection site hemolysis "compared to the same composition without magnesium." Tr. 295:5-293:12. Dr. deVries admitted, however, that pH, drug concentration, and magnesium to minocycline ratio were not the same in the tests she showed, even though these variables all affect hemolysis. Tr. 284:12-285:5. For example, the test in Figure 1 of the '802 patent compared "Mino-saline" formulations at pH 4.17, against "Mino-Mg" formulations at pH 5.85 and using a magnesium to minocycline ratio of 10 to 1. PTX 1 at Fig. 1. In Plaintiffs' mouse subcutaneous injection test, they injected in one mouse 10 mg/mL of minocycline at a pH of 2.60, and compared that to 10 mg/mL of minocycline and magnesium with a pH of 5.43. PTX 196 at MELINTA003926. None of the comparisons relates to Nexus's formulation, and then compares that same formulation without magnesium.

Third, Dr. Friedman's testimony about his personal observations are fundamentally flawed and do not show infringement. Dr. Friedman's say-so was never corroborated, as he never cited to any medical records or other patient documentation, or even himself wrote about any benefit with the new formulation. Tr. 183:25-184:13; 440:2-4; 752:5-753:20. He also never substantiated his cascade theory, that injection site hemolysis started a chain reaction of other events, which then resulted in signs and symptoms like phlebitis. Tr. 597:9-17, 632:20-23.

Finally, if the claim construction for the term "without magnesium" means "without magnesium" then the claims allow using other excipients, like calcium, in which case magnesium formulations are no better than formulations without magnesium. Tr. 412:23-413:10 (Griffith).

b) Plaintiffs failed to show indirect infringement

Without proving direct infringement, Plaintiffs cannot show indirect infringement. *Takeda*, 785 F.3d at 634; *DSU*, 471 F.3d at 1303.

Plaintiffs also failed to prove contributory infringement because they did not prove

knowledge of infringement. Nexus labeled the magnesium function in its formulation as “hemolysis reducer,” but that was based on a literature search and when specifically asked about knowledge, Dr. Tawde explained that “Nexus did not do any studies to confirm the role. So whether it is true or not, Nexus does not know. Nexus just used the literature search – literature information.” Tawde Dep. 104:7-15. And if Plaintiffs can simply assume hemolysis reduction based on Nexus’s literature search, then the same “either-or” approach for infringement and invalidity applies: the claims are invalid if injection site hemolysis is a mere inherent property of administering the claimed formulation. Plaintiffs cannot have it both ways. In addition, Plaintiffs failed to show no “substantial non-infringing uses” for dependent claims 7 and 18 of the ’802 patent, because the Nexus label allows uses Dr. deVries admitted would not infringe depending on volume or pH. Tr. 273:16-23, 274:24-275:7 (deVries).

Plaintiffs rely heavily on inducement to infringe, but, Nexus’s label is silent on hemolysis reduction. Therefore, Nexus does not encourage or instruct anyone to reduce injection site hemolysis. Dr. Friedman asserted that anyone administering the magnesium-minocycline formulation will necessarily and automatically impart an injection site reduction benefit “as a property of the formulation.” Tr. 145:11-146:1. Even if that had been proven, that still would not mean Nexus induces infringement, because Nexus does not discuss “encourage, recommend, or promote infringement.” *See, e.g., Takeda*, 785 F.3d at 631. Nexus and its product label remain entirely indifferent as to whether or not there is any reduced injection site hemolysis. To the contrary, the old Minocin label, the new Minocin label, and Nexus’s label all have the very same warnings when it comes to the key aspects that Dr. Friedman testified about: “local reactions” including “injection site erythema and injection site pain” and “thrombophlebitis.” DTX-112_0011-13, DTX-110_0008-10, PTX 42 at NEXUS-MIN-0001211-12; Tr. 182:1-13. These

warnings are identical for all the labels, showing to the public that there is no difference or benefit when it comes to using one formulation over the other. Tr. 592:24-595:10 (Chambers). The FDA rejected Plaintiffs’ request to change the label, citing insufficient evidence. DTX-72_0006. Nexus cannot induce a claim not on its label, especially where the same exact old warnings still apply.

Bayer is one Federal Circuit case that shows mere knowledge of results—even those associated with drug administration—is not enough to induce infringement without a labeled instruction related to the claims themselves. In *Bayer*, the patent covered “[a] method of simultaneously achieving” three results, one of which was contraception. *Bayer*, 676 F.3d at 1319-20. Even though no one disputed that all three results did happen when the drug was administered, defendants still did not induce infringement because there was no instruction “in any way that recommends or suggests to physicians that the drug is safe and effective for administration to patients for the purposes of inducing these effects.” *Id.* at 1322.

Allergan makes the same point, where the drug brimonidine had already been used in the prior art for reducing intraocular pressure. The asserted patent used the same drug, for the additional feature of preventing neurodegeneration. Brimonidine very well may have had both effects, but the Federal Circuit made clear that the asserted patents “do not claim the use of brimonidine for reducing IOP” because “[t]hat use, like the drug itself, is unpatented and in the public domain.” *Allergan, Inc. v. Alcon Labs*, 324 F.3d 1322, 1327 (Fed. Cir. 2003).

In *Takeda*, the defendant sought approval “for prophylaxis of gout flares,” but the claims required “treating acute gout flares.” 785 F.3d at 627-28. Even when used for prevention, defendant’s label said “if you have a gout flare while taking [the drug], tell your healthcare provider,” and FDA told the defendant “it may be natural for the provider to use [the drug] for acute treatment.” *Id.* at 630, 632. Specific intent required more: without express direction, the

evidence showed “mere knowledge of infringing uses and does not establish inducement.” *Id.*

Plaintiffs refer to other variables like pH ranges and volumes that partially changed from the old to the new label, but those are already separate claim requirements; the claims require certain pH, volume, **and** reduced injection site hemolysis. Plaintiffs invite the Court to ignore the injection site hemolysis claim term and render it meaningless, so long as pH and volume limitations are met. But to show infringement, every limitation must be proven. And Plaintiffs had every opportunity to do the work needed to justify the injection site hemolysis benefit, but never took it. Tr. 250:24-251:19 (deVries); Tr. 382:8-18 (Griffith).

3. Consisting Of (claims 1, 7, and 18 of the '802 Patent)

The claims of the '802 patent are all limited in scope because they use “consists of” language—patent parlance meaning no other ingredients can be added—but Nexus’s label will instruct adding other ingredients, so Plaintiffs cannot prove infringement. As seen above for claim construction (section IV.C.), claim 1 of the '802 patent uses the closed-ended “consists of” **three times**. With this triple-consists-of approach, Plaintiffs made sure that the formulation to be administered must only have the three listed components: water with minocycline, magnesium, and a base. As Dr. Friedman acknowledged, however, Nexus’s administered formulation will have something more: diluent components. Tr. 104:1-25. Nexus’s label requires adding these diluents which means adding unclaimed components, like sodium chloride or Lactated Ringer’s, so Nexus does not infringe the “consisting of” claims. Tr. 524:22-525:10. Because Nexus does not infringe claim 1, it cannot infringe claims 7 and 18 either. *See, e.g., Jenneric/Pentron, Inc. v. Dillon Co., Inc.*, 205 F.3d 1377, 1383 (Fed. Cir. 2000) (reiterating “fundamental principle of patent law” that “dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed”) (citation omitted).

IV. THE ASSERTED CLAIMS ARE OBVIOUS IN VIEW OF THE PRIOR ART

The Supreme Court emphasized the need for “caution” for awarding patent monopolies to “a combination which only unites old elements with no change in their respective functions.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 415-16 (2007). That is precisely what happened here. The asserted claims did nothing new. Plaintiffs simply took the old Minocin IV product, and added the excipient magnesium *because* that excipient was known to improve similar formulations. Plaintiffs’ asserted claims are invalid for obviousness under 35 U.S.C. § 103. For the reasons discussed below and as explained at trial, each of the asserted claims would have been obvious to a person of ordinary skill in the art (“POSA”) in view of the prior art, and the combination of the 2007 Minocin IV label, CN’268, and Gibbs. Tr. 511:13-18; 516:10-18.

A. **Obviousness Legal Standards**

A patent claim is invalid for obviousness under 35 U.S.C. § 103 “when the difference between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a [POSA] to which said subject matter pertains.” *KSR*, 550 U.S. at 406. Obviousness is a question of law based on underlying facts: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the prior art and the claims at issue, and (4) secondary considerations. *Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1097-98 (Fed. Cir. 2015).

Obviousness is often explained as having some “motivation” for combining prior art references with a “reasonable expectation of success” that the combination could work for its intended purpose. For motivation, there is no requirement for an express teaching, suggestion, or motivation (an abrogated “TSM test”)—although where available that can make obviousness even easier to show—as “any need or problem known in the field” can provide a reason to combine obvious elements. *KSR*, 550 U.S. at 418-420. And “[a]ll that is required is a reasonable expectation

of success” to implement the prior art combination, because “[o]bviousness does not require absolute predictability of success.” *Medichem, S.A. v. Rolabe, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (citation omitted); *see also Duramed Pharm., Inc. v. Watson Labs., Inc.*, 413 Fed. Appx. 289, 294 (Fed. Cir. 2011) (“There is no requirement that a teaching in the prior art be scientifically tested or even guaranteed success before providing a reason to combine.”)(citations omitted)).

For obviousness (35 U.S.C. § 103), unlike anticipation (35 U.S.C. § 102), there is no requirement that all of the claim elements be within one reference and applying prior art teachings to similar situations is entirely obvious. As happened here, “if a technique has been used to improve one device, and a [POSA] would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person’s skill.” *KSR*, 550 U.S. at 401. In fact, “[w]hen compounds share significant structural and functional similarity, those compounds are likely to share other properties, including optimal formulation for long-term stability.” *Valeant Pharms. v. Mylan Pharms.*, 955 F.3d 25, 32-33 (Fed. Cir. 2020).

“It is well-settled that the inclusion of an inherent, but undisclosed, property of a composition does not render a claim to the composition nonobvious.” *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020). If a property is inherent, “there is no question of a reasonable expectation of success in achieving it.” *Id.* An element is inherent for this analysis “when the limitation at issue is the “natural result” of the combination of prior art elements.” *Par Pharm., Inc. v. TWI Pharm. Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). Tacking on an inherent property to an obvious formulation does not make the resulting claim non-obvious because claiming a property associated with an obvious formulation—even if one is the first to identify that property—is not regarded as an invention. *Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999); *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir.

2012) (“To hold otherwise would allow any formation—no matter how obvious—to become patentable merely by testing and claiming an inherent property.”).

B. Person of Ordinary Skill in the Art

Patent claims are evaluated from the perspective of a POSA, a hypothetical person considered to have the skill level and knowledge of a particular field related to a claimed invention. *See Union Carbide Corp. v. Am. Can Co.*, 724 F.2d 1567, 1576 (Fed. Cir. 1984). A POSA is presumed to have before him or her all of the relevant and publicly available art at the time of the invention. The parties’ experts all agreed that their opinions will not change under any POSA definition, so the minor differences between different wordings are immaterial. Tr. 464:3-5 (Klibanov); 204:8-11 (deVries). In short, everyone includes the shared fundamental definition that a POSA should have experience formulating and/or administering pharmaceutical formulations.

C. Scope and Content of the Prior Art

No one disputes the drug minocycline had already been used intravenously to treat bacterial infections long before the asserted patents. *E.g.*, Tr. 719:18-21 (Friedman); 841:5-8 (deVries); 475:19-24 (Klibanov). Although minocycline had been around for decades, it found new appreciation in 2009, based on certain bacterial infections for which it was considered useful. *See* Friedman 707:11 (reporting return to market in 2009 due to demand from soldiers getting resistant *Acinetobacter*). By that time, intervening prior art provided guidance about how to improve the old formulation. So by May 12, 2010—the “priority date” or prior art cutoff—the prior art spelled out everything that a POSA needed to know to show the claimed inventions were obvious.

1. The Old Minocin IV product

The old Minocin IV label from 2007 taught minocycline had been FDA-approved for intravenous administration to treat various bacterial infections, including *Acinetobacter*. DTX-0112_0001, 0006-0007; Tr. 477:25-78:5 (Klibanov); 759:14-19 (Friedman); 909:2-15

(Chambers). The old Minocin IV product provided 100 mg minocycline in lyophilized form (i.e. freeze-dried solid) and had to be reconstituted in Sterile Water and then “immediately” further diluted in one of various diluents. DTX-0112_0001, 0013; Tr. 478:10-18 (Klibanov). The reconstitution volume was 5mL and the final labeled diluted formulation was between 500 and 1000mL for adults. *Id.* The old Minocin IV label further taught a weight-based dosage for pediatric patients, enabling lower volumes. DTX-0112_0013; Tr. 626:17-22, 627:2-8 (Chambers).

The old Minocin IV label taught using any of the following diluents: Sodium Chloride Injection USP, Dextrose Injection USP, Dextrose and Sodium Chloride Injection USP, Ringer’s Injection USP, or Lactated Ringer’s Injection USP. DTX-0112_0013; Tr. 479:4-18 (Klibanov). When diluted in Lactated Ringer’s, the old Minocin IV label taught that minocycline would be administered at pH 4.5-6.0. *Id.*; *see also* Tr. 728:3-6 (Friedman). When diluted in other diluents such as saline or dextrose, the old Minocin IV label taught the pH would be 2.5-4.0.

2. CN’268 Taught Adding Magnesium To Improve Solubility, Stability, and Tolerability of Parenteral Tetracycline Formulations

Prior art CN’268 (DTX-0014) taught that adding magnesium to an aqueous parenteral doxycycline formulation would provide several benefits, because as Dr. Klibanov explained, it reported “adding magnesium, which forms a complex with this tetracycline antibiotic, achieves higher solubility and stability in particular at higher pH values, and also reduces toxicity and tissue irritability upon injection.” Tr. 484:5-17. CN’268 expressly taught that adding magnesium ions at “higher content” to a tetracycline improved concentration, pH, and irritability issues—the same concerns Plaintiffs’ experts said a POSA faced with the old Minocin IV product. DTX-0014_0005 at [0006]; Tr. 484:4-17, 486:1-6 (Klibanov); 842:20-843:16 (deVries). CN’268 specifically tied these benefits to magnesium in particular, reporting magnesium “creates a complex with the doxycycline to (1) “increase the solubility and pH”, (2) “enhanc[e] the stability of the injection,”

and (3) reduce “toxicity and tissue irritability.” DTX-0014_0005 at [0006]. Because these benefits were expressly attributed to the magnesium-tetracycline complex, Dr. Klibanov explained that CN’268 taught adding magnesium ions to a minocycline intravenous formulation would improve stability and solubility, particularly at higher pH values, and also would reduce toxicity and tissue irritability. Tr. 489:1-7. Dr. Chambers explained that the “toxicity and tissue irritability” benefit includes blood and skin issues such as phlebitis or thrombophlebitis. Tr. 622:24-623:11.

CN’268 taught that its formulation could be prepared within the range of pH 3.0-7.0, and that this pH could be adjusted using a base. DTX-0014_0004 at [0004]; Tr. 486:8-18 (Klibanov). Dr. Chambers explained that CN’268 even administered the drug to animals and reported positive results. Tr. 624:12-625:5. CN’268 was not before the Patent Office during patent prosecution. Tr. 511:20-512:1 (Klibanov); 846:5-10 (deVries).

3. Gibbs Taught Adding Magnesium to Doxycycline or Minocycline in Molar Ratios up to 8:1

Prior art Gibbs taught parenteral formulations of either doxycycline or minocycline with magnesium, and further taught using molar ratios of up to 8:1 magnesium to minocycline. DTX-0012_0002; Tr. 490:8-14 (Klibanov). These molar ratios represent using more magnesium than minocycline, consistent with the “higher content” of magnesium suggested by CN’268 for its doxycycline formulation. Tr. 492:5-13 (Klibanov). The Gibbs formulations were used to treat chlamydia trachomatis, a particular bacterial infection, in animals including humans. DTX-0012_0001 at 1:3-5. Also like CN’268, Gibbs taught that magnesium forms “chelates” or complexes with minocycline. Tr. 491:16-20 (Klibanov); DTX-0012_0003 at 3:29-31.

Gibbs further disclosed 100mg of minocycline or doxycycline in the formulation, the same dosage as in the old Minocin IV product. DTX-0012_0002 at 2:30-32; Tr. 490:15-18 (Klibanov). The administered volume of the Gibbs formulation was 5mL, showing that very high

concentrations (100 mg/5 mL is 20 mg/mL) were easily obtained using magnesium-minocycline formulations. DTX-0012_0002 at 2:19-21; Tr. 490:19-21 (Klibanov). Further, Gibbs taught the pH of its formulation was between 5.0-7.0, and that this pH could be achieved by adding a base as needed. DTX-0012_0003 at 3:60-4:6; Tr. 493:14-23 (Klibanov).

D. Difference between the prior art and the claims at issue

There is very little difference between the prior art and the asserted claims. As Dr. Klibanov explained at trial, the prior art Minocin IV label covered all the claim elements other than magnesium; CN'268 and Gibbs would have motivated a person of ordinary skill to add magnesium at an excess molar ratio and optionally a base to increase pH; and the claimed osmolality and injection site hemolysis were already expected in view of the prior art, which Plaintiffs assert they are inherent results anyway. Tr. 504:18-22, 506:3-10; 512:4-10, 512:17-513:4 (Klibanov).

1. CN'268 and Gibbs explained how and why to add magnesium to Minocin IV to improve the formulation.

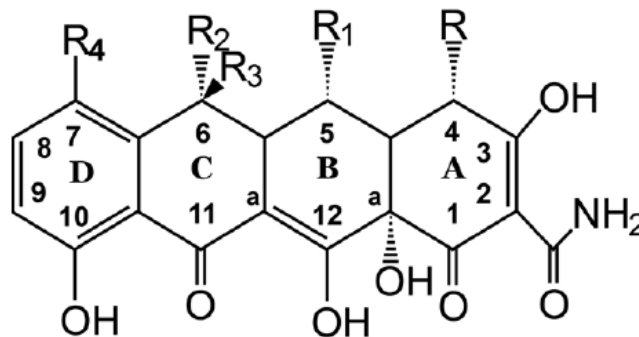
As of the priority date, Minocin IV taught how to use intravenous minocycline, CN'268 already explained why magnesium should be added, and Gibbs already explained how much to add. Plaintiffs point out that CN'268 used doxycycline, but a POSA would know that doxycycline is structurally related to minocycline and therefore relevant.

First, as explained above and by Dr. Klibanov at trial, CN'268 expressly reported that adding magnesium to a tetracycline formulation increased pH, increased concentration, and improved tolerability. Tr. 483:7-484:17; *see supra* at [IV.C.2]. These improvements line up precisely with the reasons Plaintiffs' own experts admit a POSA would have been motivated to improve the prior art Minocin IV product. For example, Dr. deVries admitted there was "motivation to increase the pH of the old Minocin formulation" (Tr. 843:2-5); "motivation to decrease side effects related to the old minocycline formulation" *i.e.* improve tolerability (Tr.

843:6-16); and motivation to decrease the volume of administration because “it’s a generally accepted principle that you want to have a smaller injection volume when you’re administering medication” in the prior art. Tr. 842:24-843:1.

Second, Gibbs confirmed the relevance of doxycycline formulations to minocycline formulations by using the two drugs interchangeably. Gibbs showed examples using doxycycline, but represented throughout the patent that the same formulation approach worked for minocycline too, and claimed using the same formulation for either compound. Klibanov 491:16-492:4. The scientific principle was identical to that reported in CN’268: “Magnesium ions react with doxycycline and minocycline to form, respectively, magnesium-doxycycline and magnesium-minocycline chelates.” DTX-0012_0003 at 3:29-31.

Third, a POSA understood the chemical structures for doxycycline and minocycline were very closely related. Tr. 683:1-19 (Chambers). Minocycline is a member of a class of antibacterial drug compounds known as tetracyclines. Tr. 470:15-19 (Klibanov). As of the priority date, tetracyclines were well known to have the following shared chemical structure:



Shared chemical structure of tetracyclines

Tr. 470:15-472:19 (Klibanov); DDX-2010. This common tetracycline structure comprises four fused rings (labeled A-D) made up of 12 carbon atoms (locations identified by numbers 1-12). *Id.* The four rings explain the name “tetra-cycline.” *Id.* While the various tetracycline compounds

have differences at the locations depicted above by the letter R, they share all the remaining structure, including the bottom half of the molecule as shown (along the numbers 10-11-12-1). *Id.*

The focus on the bottom half is important because a POSA would have known magnesium binds in that region, which is identical as between doxycycline and minocycline. Tr. 497:8-18; 475:1-14 (Klibanov). The prior art taught magnesium formed complexes or chelates when combined with minocycline or other tetracyclines specifically along that shared bottom half. *See, e.g.,* Nelson 1998 (DTX0174; PTX151); Barringer (DTX0172; PTX152); Berthon (DTX0183); Gibbs (DTX0012). Both parties relied on prior art Nelson 1998, which explained that magnesium complexation of tetracyclines had been studied extensively before the priority date, and that magnesium was known to bind with tetracyclines at the C-11 and C-12 locations, which are on the bottom half of the compound and “exactly the same” for doxycycline and minocycline. DTX-0174_0004; Tr. 495:23-496:23, 497:8-18 (Klibanov). Moreover, prior art Berthon studied magnesium binding for tetracyclines, and concluded there is a “striking similarity” between magnesium-doxycycline and magnesium-minocycline. DTX183_0005; Tr. 884:7-17 (deVries).

2. The Prior Art Taught Administration of Minocycline in Volumes below 500mL.

Claim 18 of the '802 patent contains a volume requirement (“less than 500 mL”) but POSAs already used the old Minocin IV product at volumes in that range. For example, the old Minocin IV label taught administration in less than 500mL for pediatric patients. Tr. 626:17-22; 627:2-8 (Chambers). Additionally, Plaintiffs admitted to FDA that volumes “ranging between 100 mL and 500 mL” had already been used and presented eleven prior art articles in support. DTX-0072_0008; Tr. 754:24-755:7 (Friedman). Plaintiffs relied on these articles precisely to show FDA that lower administration volumes were already commonplace, and thus justified the changed volume range on the label. Tr. 754:8-18 (Friedman).

Additionally, a POSA would have known how to use reduced volumes of the old Minocin IV product below 500mL applying CN'268 (which taught increasing drug concentration with magnesium) and Gibbs (which even gave an example down to 5 mL). Tr. 625:23-626:1 (Chambers); 510:18-25 (Klibanov). Both CN'268 and Gibbs taught how to improve solubility of the tetracycline compound, which allows for higher concentration and thus lower volume for a given dosage. *See* Tr. 483:15-25, 467:23-468:4 (Klibanov). The 5mL example for 100mg minocycline (the same 100mg dose as in the old Minocin IV product) showed using low volumes was easily achievable. DTX-0012_0002 at 2:19-33; Tr. 490:15-21 (Klibanov). Especially given that the prior art labeled range for adults included "500 mL" and the claim is for any amount less than 500 mL, this claim limitation would have been insignificant to a POSA.

3. The Prior Art Taught Administration of Minocycline Within the pH Ranges Claimed.

All claims provide pH ranges, though the ranges vary between 4-6, 4.5-5.5, and 4-7. Experts for both parties agreed that the old Minocin IV product taught administering a formulation within the pH range of 4.5-6.0 when diluted in Lactated Ringer's, or 2.5-4.0 if prepared in other diluents. DTX-0112_0013; Tr. 480:10-17 (Klibanov); 728:3-6 (Friedman). Thus, for the case of Lactated Ringer's, the prior art pH already matched the claimed ranges. Even for the other diluents, which had slightly lower administered pH ranges, CN'268 taught that adding magnesium helped increase pH and reported that its formulations could be administered within the pH range of 3.0-7.0. DTX-0014_0004 at [0004]; Tr. 486:7-19 (Klibanov). Gibbs also taught administered formulations at pH 5.0-7.0. DTX-0012_0003 at 3:60-4:6; Tr. 493:14-18 (Klibanov). These references showed a POSA could easily achieve the claimed pH ranges by adding magnesium. Even under Plaintiffs' erroneous claim construction focusing on the reconstituted intermediate, applying the same prior art would increase reconstituted pH in the same way in the claimed range.

E. Summary of Obviousness

The prior art Minocin IV label already taught how to intravenously administer an aqueous formulation of minocycline to treat bacterial infections. CN'268 and Gibbs taught adding magnesium to improve characteristics of aqueous tetracycline formulations such as minocycline including solubility, stability, and tolerability, providing a POSA with a motivation and reasonable expectation of success to achieve the claimed invention. Tr. 500:15-501:3 (Klibanov).

1. A POSA Would Have Been Motivated By the Prior Art to Add Magnesium to the Old Minocin IV Product.

While express motivation is not required, CN'268 outlined the key benefits for adding high ratios of magnesium in tetracycline formulations. Tr. 489:1-7 (Klibanov). As explained above, those were the very same benefits Plaintiffs admitted that a POSA would have sought to improve. *See supra* at IV.D.1. As Dr. Klibanov explained at trial, a POSA looking to modify the prior art Minocin IV product would have looked to CN'268 and Gibbs because they dealt with improving tetracycline formulations, and the two closely-related minocycline and doxycycline tetracyclines in particular. Tr. 482:6-16, 489:8-12 (Klibanov).

2. A POSA Would Have Had a Reasonable Expectation of Success

Given the fact that the prior art including CN'268 and Gibbs actually made tetracycline formulations using high magnesium ratios, and the similarity of doxycycline and minocycline, *see supra* at IV.D.1, a POSA would have had a reasonable expectation of success of making the claimed minocycline-magnesium formulations. Tr. 500:15-501:3 (Klibanov).

F. Claim-By-Claim Analysis: The Asserted Claims are Invalid as Obvious In View of the Old Minocin IV Label, CN'268, and Gibbs

Having shown the motivation to combine and reasonable expectation of success, here Nexus applies the prior art teachings in detailed fashion to each and every claim limitation.

1. The '802 patent claim 1

- a) “A method of treating a bacterial infection in a subject, wherein the method consists of: administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration”**

There is no dispute that using intravenous minocycline to treat bacterial infections was already known in the prior art, including of course the 2007 Minocin IV label. *See* Klibanov 506:13-507:12; *see supra* at IV.C.1. Minocin IV was already an intravenous product. Both Dr. Klibanov and Dr. Chambers also explained that parenteral formulations such as intravenous and intramuscular formulations have similar considerations that would have directed a POSA to consider intramuscular references in modifying an intravenous formulation. For example, Dr. Klibanov explained that both are aqueous formulations that differ only at the destination of the injection, so relevant characteristics are similar. Tr. 487:6-12. Dr. Chambers explained intramuscular formulations informed a POSA regarding IV tolerability because one “would expect [reduced] toxicity at the site of injection [in an IM formulation] would translate to improved tolerability if given intravenously.” Tr. 623:12-23.

- b) “wherein the composition consists of an aqueous solution consisting of minocycline or a salt thereof, a salt that comprises a magnesium cation, and a base,”**

As explained above and by Dr. Klibanov, the old Minocin IV label taught using minocycline hydrochloride in solution and CN'268 and Gibbs would have motivated a POSA to add a magnesium cation and base with a reasonable expectation of success, because it was shown to work to improve injectable formulations. Tr. 507:14-508:2.

- c) “wherein the molar ratio of magnesium cation to minocycline is greater than about 4:1, and”**

As explained above and by Dr. Klibanov at trial, the claimed magnesium molar ratio range was obvious based on the prior art and a POSA's knowledge. Gibbs taught molar ratios up to 8:1,

which overlaps with the claimed 4:1 range, and would have motivated a POSA to prepare formulations within the molar ratio with a reasonable expectation of success. Tr. 508:4-9. Gibbs was not the only reference that taught high molar ratios of magnesium to tetracycline above 4:1, so it is not as if Plaintiffs broke some known barrier by using ratios that were already in the prior art. Tr. 493:25-494:15 (discussing DDX2015).

For range claims like this one, “[a] prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.” *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003); *see also UCB v. Actavis*, 65 F.4th 679, 687 (Fed. Cir. 2023); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006).

As a separate and independent basis for showing obviousness, a POSA would have been able to identify a suitable molar ratio of magnesium to minocycline within the claimed ranges using nothing more than routine optimization. Dr. deVries admitted that a POSA would have known how to run experiments with varying the magnesium to minocycline molar ratio, to assess characteristics such as solubility. Tr. 889:2-9. Dr. Klibanov also explained it would be simply routine experimentation to optimize the concentration of the magnesium and the ratio of magnesium to the corresponding antibiotic. Tr. 494:23-495:2. The longstanding rule set by the Federal Circuit’s predecessor court thus applies: “it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456 (CCPA 1955).

d) “wherein the composition has a pH that is no less than 4 and no greater than 6,”

As explained above and by Dr. Klibanov at trial, each of the 2007 Minocin IV label, CN’268, and Gibbs taught formulations prepared in overlapping pH ranges and would have motivated a POSA to prepare formulations within this range with a reasonable expectation of success. Tr. 508:11-13, 18-23. For claim construction, Plaintiffs dispute whether this pH should

refer to a reconstituted intermediate or the diluted formulation that is administered, but both are obvious in view of the prior art because Gibbs and CN'268 each taught increasing formulation pH by adding magnesium and base, just like the claimed invention.

The prior art Minocin IV product itself (4.5-6.0 for Lactated Ringer's and 2.5-4.0 for other diluents) already included and overlapped with the claimed pH range (4-6), so as discussed above for the molar ratio ranges, a presumption of obviousness applies. *In re Peterson*, 315 F.3d at 1329; *UCB*, 65 F.4th at 687; *Ormco*, 463 F.3d at 1311. Even the reconstituted pH of the prior art Minocin IV product had a pH range of 2.0 to 2.8, which was never administered without diluting to a higher pH, but in any event experts from both parties agreed that a POSA would seek to increase pH where possible for the purpose of administering drug closer to physiological pH for tolerability purposes. *See, e.g.*, Tr. 468:24-469:7 (Klibanov); 852:19-25 (deVries); 643:17-20 (Chambers); 697:25-698:5, 699:3-7 (Friedman). A POSA would have known all of these were easily achievable, in view of CN'268 (pH 3.0-7.0) and Gibbs (pH 5.0-7.0). Tr. 508:18-23 (Klibanov).

As a separate and independent basis for obviousness, a POSA would have been able to identify a suitable pH within the claimed ranges using routine experimentation. *In re Aller*, 220 F.2d at 456. Plaintiffs' expert Dr. deVries admitted that a POSA would have known how to run experiments with varying pH or concentration to assess characteristics such as solubility ratio. Tr. 889:2-9. Further, Dr. Klibanov explained the basic step of adjusting pH of a formulation would have been well within the everyday skill set of a POSA. Tr. 469:8-14.

- e) **“whereby injection site hemolysis of red blood cells is reduced relative to intravenous administration of a composition that does not include magnesium.”**

Plaintiffs' experts Drs. deVries and Friedman asserted that this limitation would occur every time, as a result of administering the claimed formulation. Tr. 230:5-8 (deVries); 768:25-769:2 (Friedman). If it is shown to be reduced at all, then reducing injection site hemolysis is an

inherent property, because no additional steps beyond mere administration of the claimed formulation is needed to achieve the claimed result. Tr. 229:21-230:2 (deVries); 505:20-506:10 (Klibanov). If an element is inherent such as where “the limitation at issue is the ‘natural result’ of the combination of prior art elements,” then the limitation does not need to be separately addressed when showing obviousness. *Par*, 773 F.3d at 1194-95; *Hospira*, 946 F.3d at 1332 (“It is well-settled that the inclusion of an inherent, but undisclosed, property of a composition does not render a claim to the composition nonobvious.”).

In the alternative, even if not an inherent property, Nexus showed at trial that any reduced injection site hemolysis limitation would have been obvious to a POSA in view of the prior art. A POSA would have expected this result based on the teachings in CN’268 that adding magnesium would reduce toxicity and tissue irritability of the drug. Tr. 509:1-4, 9-17 (Klibanov); 622:20-623:23 (Chambers); DTX-0014_0005 at [0006]. The improved tolerability would have been even more obvious based on Plaintiffs’ expert testimony that increasing pH by itself improves tolerability. Tr. 117:5-20, 697:25-699:7, 761:11-14 (Friedman); 845:4-12 (deVries). Thus, this limitation would have been obvious in view of the prior art even if not inherent.

2. ’802 patent claim 7: The method of claim 1, wherein the composition has a pH between about 4.5 to about 5.5

Claim 7 of the ’802 patent uses the pH range 4.5-5.5 instead of the slightly broader 4.0-6.0 from claim 1. Claim 7 is invalid in view of the prior art for at least the same reasons explained above for claim 1. No evidence or testimony suggested this range was special compared to the other claimed pH ranges, they were all viewed as the same. As explained above and by Dr. Klibanov at trial, each of the 2007 Minocin IV label, CN’268, and Gibbs taught formulations with overlapping pH ranges and would have motivated a POSA to prepare formulations within this range with a reasonable expectation of success. Tr. 510:3-11. Whether this pH refers to the

reconstituted intermediate or the diluted formulation that is administered, both were obvious for the reasons explained above. Achieving this pH was nothing more than routine optimization as well, especially since the prior art commercial formulation already taught administering this pH range with Lactated Ringer's and up to pH 4.0 with every other diluent. The tweak from 4.0 to 4.5 was entirely obvious in view of the prior art.

3. '802 patent claim 18: The method of claim 1, wherein the total volume of the composition administered is less than 500 mL.

Asserted claim 18 of the '802 patent adds a requirement to claim 1 that the composition volume must be less than 500 mL, but lower volumes were already used so there is nothing new, and adding magnesium only made it easier to use lower volumes. For this "composition" claim term, parties agreed that it means the administered volume.

First, as Plaintiffs' expert Dr. Friedman admitted, the prior art articles acknowledged by Plaintiffs to FDA showed clinical use of 100-500mL volumes, which matches claim 18's volume limitation. Tr. 755:14-18. Dr. Chambers also testified that the prior art Minocin IV label already taught using volumes less than 500mL when used for children, so that the low volumes were already in use for this population, and that testimony was unrebutted. DTX-0112_0013; Tr. 626:17-22, 627:2-8. Thus there is no difference between this claim limitation and what was already done the prior art—even before adding magnesium.

Second, as explained above, experts for both parties explained a POSA would have been motivated to reduce the volume of administration reported for the old Minocin IV product. Plaintiffs' expert Dr. Friedman further testified a POSA would have known how to adjust volume, administration rate, and dosing to match the existing known therapeutically effective amount from the old Minocin IV product. Tr. 100:25-101:6. Dr. Friedman further testified the reduced volume was a result of "normalizing" pH, meaning a POSA would have expected that simply permitting

for adjusted pH would reduce the volume required for administration. Tr. 755:9-13; 121:18-23. Because increasing pH was already obvious in view of the prior art by adding magnesium as discussed above, so too was reduced volume.

Third, Dr. Klibanov explained at trial that increasing the solubility of tetracycline in a formulation allows increased concentration, which mathematically equates to a lower volume for a given dosage. Tr. 485:21-25. Because the prior art taught using magnesium to increase solubility, it would have been obvious to a POSA to increase minocycline concentration and use administration volumes less than 500mL. Tr. 510:18-511:12.

4. The '105 patent claim 27

Each limitation of claim 27 and claim 1 from which it depends is addressed below.

- a) **A method of treating a bacterial infection in a subject, wherein the method comprises administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration,**

As above, there is no dispute that the prior art showed minocycline treated bacterial infections, including the 2007 Minocin IV label. *See* Tr. 513:7-24.

- b) **wherein the composition comprises an aqueous solution of a 7-dimethylaminotetracycline antibiotic [minocycline] and a magnesium cation,**

Claim 1 refers to a general group of any “7-dimethylaminotetracycline” and claim 27 specifies that the compound must be “minocycline.” As explained above and by Dr. Klibanov, the old Minocin IV label taught using minocycline, and CN’268 and Gibbs would have motivated a POSA to add a magnesium cation with a reasonable expectation of success. Tr. 514:1-14.

- c) **wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and**

As explained above and by Dr. Klibanov at trial, Gibbs and other prior art references taught use of molar ratios up to 8:1, which overlaps with the claimed range, and would have motivated a

POSA to prepare formulations within the molar ratio or at least perform routine experimentation to do so with a reasonable expectation of success. Tr. 514:15-17.

d) wherein the solution does not comprise a pharmaceutically acceptable oil,

As explained above and by Dr. Klibanov at trial, neither the 2007 Minocin IV label nor CN'268 contained a pharmaceutically acceptable oil, so a POSA already would not understand one to be necessary for minocycline formulations (Minocin IV) or for making magnesium work (CN'268). Tr. 514:19-25. Gibbs used oil in its formulation, but as Dr. Klibanov and Chambers explained, also disclosed why it was using oil: to facilitate the intramuscular nature of the formulation, which would not be useful for an IV formulation, and a POSA generally would not want to use oil in an intravenous formulation. Tr. 492:17-493:12 (Klibanov); 619:5-620:10 (Chambers). Thus, a POSA would know how to apply Gibbs and not use oil for an IV formulation. Tr. 492:17-21 (Klibanov); 622:5-13 (Chambers).

e) has a pH greater than 4 and less than 7, and

As explained above and by Dr. Klibanov at trial, each of the 2007 Minocin IV label, CN'268, and Gibbs taught formulations prepared in overlapping pH ranges and would have motivated a POSA to prepare formulations within this range with a reasonable expectation of success. Tr. 508:11-13, 18-23.

f) has an osmolality less than about 500 mOsmol/kg.

As discussed above for injection site hemolysis, so too here Plaintiffs' experts assert that the osmolality limitation is an inherent property, and opined that all administered formulations have an osmolality less than 500 mOsmol/kg. Osmolality is a measure of the concentration of dissolved substances. Tr. 469:16-20 (Klibanov); 233:25-234:13 (deVries). While the parties disagree for claim construction whether the term applies to the reconstituted vial or the diluted IV

bag, experts from both parties agreed that osmolality is a function of the components of a formulation. Tr. 634:4-21 (Chambers); 512:11-13, 512:25-513:4 (Klibanov); 253:10-19 (deVries). And under Plaintiffs' experts' view that the osmolality was always under 500 mOsmol/kg as an inherent property of the formulation (*e.g.* Tr. 253:10-17, 259:9-12), no additional proof is needed to show obviousness. *See, e.g., Par*, 773 F.3d at 1194-95; *Hospira* 946 F.3d at 1332.

In the alternative, even if not an inherent property, Nexus showed at trial that the claimed osmolality would have been obvious to a POSA in view of the prior art because it was standard practice. Tr. 470:4-8, 512:11-24, 515:16-516:9 (Klibanov); 627:24-628:1 (Chambers); DTX-0175. Plaintiffs' experts agreed. Tr. 308:6-9 (deVries); 762:16-19 (Friedman). Dr. deVries even testified that osmolality for both the reconstituted and diluted versions of the old Minocin IV product was already known or expected to be less than 500 mOsmol/kg. Tr. 841:9-24. Thus, whether inherent or not, this limitation would have been obvious.

G. There Are No Secondary Considerations Weighing Against Obviousness

1. Secondary Consideration Legal Standards

Plaintiffs bear the burden of production with respect to evidence of any alleged secondary considerations. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1354 (Fed. Cir. 2013). In other words, the patentee must present evidence to support a finding that a given secondary consideration exists and is relevant. *See, e.g., Hospira, Inc. v. Amneal Pharm., LLC*, 285 F. Supp. 3d 776, 784 (D. Del. 2018) (*citing Apple Inc. v. Samsung Elec. Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016)). To be relevant, Plaintiffs must demonstrate a nexus, or connection, between the claims and the proposed secondary consideration. Where the offered secondary consideration may be attributed to something other than what is both claimed and novel, there is no nexus to the merits of the claimed invention. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Secondary considerations cannot overcome a strong *prima facie* showing of obviousness,

such as shown in this case. “Given the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate to overcome a final conclusion that [the claim] would have been obvious.” *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007); *see also Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013) (“[W]here a claimed invention represents no more than the predictable use of prior art elements according to established functions...evidence of secondary indicia are frequently deemed inadequate to establish non-obviousness.”); *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006) (“Secondary considerations of nonobviousness are insufficient as a matter of law to overcome” obviousness.).

2. Plaintiffs Have Not Established Any Long Felt Need

Plaintiffs allege there was a “long felt need” for an improved intravenous formulation of minocycline. This allegation requires supporting evidence, because mere assertions without “evidence to explain how long this need was felt, or when the problem first arose” or “evidence show[ing] that [the patent] met any such ‘need’” are not enough. *Perfect Web Techs. Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332-1333 (Fed. Cir. 2009). But Plaintiffs identify no demand for the claimed invention beyond the self-serving testimony of Dr. Friedman. *See, e.g.*, Tr. 184:25-184:12 (Friedman). They have no journal articles, no news reports, no consumer surveys, no opinion articles, and not even any database reports regarding any issue with the old Minocin IV product formulation. Tr. 752:5-753:20 (Friedman). These are critical failures. *See In re Kahn*, 441 F.3d 977, 990-91 (Fed. Cir. 2006) (law “requires that [patentee] submit actual evidence of a long-felt need, as opposed to argument”).

Plaintiffs also had to show their product actually solved whatever long-felt need they allege. But Plaintiffs did not: there is virtually no difference in how the old and new Minocin IV products are used today. In fact, Dr. Chambers confirmed the product labels are generally “the

same.” Tr. 581:10-23. The administration procedure did not change, and safety and efficacy did not change either. Tr. 608:7-609:2 (Chambers). Plaintiffs’ expert Dr. Friedman claims there was a long-felt need for a better tolerated formulation. Tr. 708:18-24. But as explained above, the label states no benefits or advantages, and never references hemolysis or osmolality, so there is no nexus between the claims and any supposed long-felt need. In addition, the old Minocin IV label already taught an administered pH that matches the current formulation when using Lactated Ringer’s diluent. While Plaintiffs’ expert Dr. Friedman claims use of Lactated Ringer’s was not actually used in practice, that misses the point: the pH was already known in the prior art. Friedman 727:14-19. “Where the differences between the prior art and the claimed invention are... minimal...it cannot be said that any long-felt need was unsolved.” *Geo M. Martin Co. v. Alliance Machine Sys. Intern. LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010).

Finally, Plaintiffs have not established evidence of any “long felt” time period. *See Perfect Web*, 587 F.3d at 1332-1333. According to Dr. Friedman, the long-felt need was based on minocycline’s ability to treat certain resistant bacterial strains. *See* Tr. 708:18-24. Dr. Friedman admitted, however, this need was met by the return of the old Minocin IV formulation in 2009. Tr. 707:11-708:8. Thus at most, Plaintiffs’ definition of the alleged need began only in 2009—mere months before the priority date of the asserted patents.

3. There Is No Such Thing As A Passage Of Time As A Standalone Secondary Consideration

“Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness.” *Iron Grip Baseball Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004)). That is because evidence of non-obviousness must be something that suggests there was a technical barrier or challenge to making or using what is now claimed. Otherwise, there is no showing of a secondary consideration relevant to help show

claims are obviousness or non-obviousness, as opposed to a showing that something simply had not been done. For example, the long passage of time by itself could just as well show that particular patent objectives were not really needed at all, which is consistent with the evidence in this case. And as explained above, Plaintiffs' argument overlooks the fact that there really was no long passage of time in the window after Gibbs, CN'268, and the resurgent use of old Minocin IV.

4. Plaintiffs Have Not Established Any Surprising or Unexpected Results by the Claimed Formulations

While Plaintiffs refer generally to higher pH and lower volume as an unexpected result, they fail the nexus requirement because no claims are limited to these features, and in fact only one claim mentions volume at all. In addition, the benefit that using the claimed magnesium ratios enabled higher pH and lower volume was hardly unexpected, because that very benefit was spelled out in the prior art. CN'268 expressly taught that adding magnesium to a tetracycline would create a complex to improve stability and solubility at increased pH, and also would improve injection site tolerability. DTX-0014 at [0006]. As explained above, CN'268 taught similar formulations of doxycycline with magnesium at pH 3.0-7.0 and Gibbs taught formulations of minocycline with magnesium at pH 5.0-7.0. DTX-0014 at [0004]; DTX-0012 at 3:60-63. Both taught formulations could be parenterally administered, meaning to a POSA that it took into account stability and solubility concerns at these pH ranges, which are consistent with the claimed pH ranges.

In addition, any differences between the prior art are minor differences in degree, which cannot lend weight as a secondary consideration. *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (explaining evidence of unexpected properties reflecting a "difference in degree" rather than "difference in kind," i.e., a new property dissimilar to the known property, cannot overcome obviousness). The claim scope differences are minor, comparing the pH 4.5 versus the pH 4.0 already in the prior art even for

diluents other than Lactated Ringer's, and the volume "less than 500 mL" compared to 500 mL even on the prior art label and actual uses with less than 500 mL again already in the prior art.

5. Plaintiffs Have Not Established Any Teaching Away

For teaching away, it is clear from the references themselves that they j never actually taught away from the claimed invention. As a preliminary matter, every "teaching away" reference cited by Plaintiffs was dated before Gibbs and CN'268, and thus could not teach away from their disclosures. *See* Tr. 847:7-25, 849:6-14 (Pawelczyk), 849:23-850:1 (Berthon); 849:15-22 (Barringer); 850:2-6 (Allen) (deVries). In addition, none of the references cited by Plaintiffs' experts actually "criticize, discredit, or otherwise discourage investigation" into the claimed formulation and thus cannot meet the standard for teaching away. *Galderma Lab's, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (citation omitted).

Pawelczyk reported aqueous solutions of minocycline at pH 4.2 and 5.2 worked, retaining "90% of their original activity at 7 days at 25°C." PTX133 at 409; Tr. 898:7-20 (deVries). That is already within the pH range of the asserted claims—without adding magnesium. So no one would be discouraged from using the claimed ranges, all of which include pH 5.2. And importantly, Pawelczyk never discouraged combining magnesium with minocycline, instead confirming that magnesium was one of the metal cations that did **not** harm minocycline. PTX133 at 417.

Similarly, deVries 2006, which unlike all of Nexus's references, is directed to **oral** formulations—so could not have taught away for injectable formulations. Melinta itself distinguished deVries 2006 as irrelevant for the same reason. Tr. 874:11-875:13 (deVries). Nevertheless, even deVries 2006 taught solutions of minocycline and magnesium could be prepared within the claimed pH ranges. *See, e.g.*, DTX-0010 at [0070] (reporting suspension does not occur until "final pH in the range of from about 5 to less than about 8").

Dr. deVries also pointed to selected snippets from Barringer (PTX152), Allen (PTX157), and Berthon (PTX 158) to suggest teaching away, but the snippets only told part of the story. For example, Dr. deVries testified that Barringer concluded minocycline should not be formulated or co-administered with high concentrations of metal cations. Tr. 777:16-23, 787:21-788:21. As Dr. Klibanov explained, however, this statement in Barringer warned only about absorption of oral formulations, and had nothing to do with intravenously administered formulations. Tr. 914:7-915:19. Dr. deVries's citation to a statement in Allen that she in turn reported as citing to Barringer and providing the "the same message" similarly does not teach away for the same reasons. Tr. 790:12-19. Finally, Dr. deVries cited to Berthon showing minocycline and magnesium would see precipitation at increasing pH, Tr. 789:25-790:8, but that phenomenon remains true to this day and depends on how high the pH is raised. In fact, precisely because of this concern, Nexus for lack of written description and enablement (as discussed below) pointed out the same problem since the claims purport to cover pH ranges up to 7.0. For the lower pHs within the claimed ranges, there was no teaching away, so in addition to the absence of proof, there is no nexus between the teaching away assertions and the scope of what was actually claimed.

6. Plaintiffs Have Not Established How Any Alleged "Copying" Could Suggest Non-Obviousness

Plaintiffs also allege copying, but any alleged copying has little relevance to obviousness in FDA submission cases such as this one where ANDA filers are required by law to establish equivalence to the reference drug product. *See, e.g., Bayer Healthcare Pharmaceuticals, Inc. v. Watson Pharmaceuticals, Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013). Dr. deVries admitted that the Nexus ANDA product was required to have the same active and inactive ingredients in the same amounts as Plaintiffs' Minocin IV product for *regulatory* reasons. Tr. 205:24-206:21.

Plaintiffs allege Nexus could have pursued an alternative regulatory route to seek approval

from FDA for the old Minocin product. However, Plaintiffs fail to support this allegation as a viable alternative. Plaintiffs never explained how Nexus could have used the old Minocin IV product as a reference standard since it was not on the market, though Nexus would have had to run tests comparing against the old product. *See* Tr. 304:1-5, 902:5-11 (deVries). In addition, Dr. deVries admitted she did not know why Nexus used one formulation over the other. Tr. 901:7-12.

V. THE ASSERTED CLAIMS ARE INVALID UNDER 35 U.S.C. § 112

Section 112 of the Patent Act exists to make sure patent claims match up to clear boundaries and are supported by the patent specification. If not, the claims are invalid.

A. Section 112 Legal Standards

1. Indefiniteness

If a claim's boundaries are not properly defined, then the claim is invalid as indefinite. 35 U.S.C. § 112 requires a patentee to particularly point out and distinctly claim the subject matter that she regards as her invention. The test is whether a claim "fail[s] to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). Indefiniteness is "a question of law." *Teva Pharma. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015).

2. Lack of Enablement

If a claim covers a broad range but the specification only shows a subset that actually works for its intended purpose, then the claim is invalid for failing the written description and enablement requirements. Section 112 requires a patent specification to provide sufficient information to allow a POSA to make and use the claimed invention. The Supreme Court has recently confirmed, "if our cases teach anything, it is that the more a party claims, the broader the monopoly it demands, the more it must enable." *Amgen Inc. v. Sanofi*, 143 S.Ct. 1243, 1256 (2023). "Claims are not enabled when, at the effective filing date of the patent [a POSA] could not practice their full scope

without undue experimentation.” *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). Full scope enablement requires enough disclosure in the specification to justify the breadth of the claim. *See Trustees of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1363-65 (Fed. Cir. 2018) (holding enablement of five out of six permutations of the claimed invention is not full scope enablement). Enablement is a question of law based on underlying facts. *See, e.g., Wyeth & Cordis*, 720 F.3d at 1384.

3. Lack of Written Description

35 U.S.C. § 112 further requires that a patent cannot claim more than it describes. “The test for [written description] is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (citation omitted). Written description is an issue of fact. *Ariad*, 598 F.3d at 1351.

B. Claims 1, 7, and 18 of the ’802 Patent Are Invalid for Indefiniteness Because “Injection Site Hemolysis” And Cannot Be Measured.

Every asserted claim of the ’802 patent requires that “injection site hemolysis” is reduced as compared to a minocycline formulation without magnesium. But the patent nowhere defines what that phrase means, and no one at trial could point to any reference describing it. As Dr. Chambers explained, even though *hemolysis* is a known term, *injection site* hemolysis is not. Tr. 596:17-20. Plaintiffs’ own experts also could not agree on this term. Dr. Friedman never explained how to measure injection site hemolysis, and instead pointed to other “downstream blood flow issues” that allegedly cause other “consequences,” such as “venous phlebitis.” Tr. 114:4-115:2; 115:19-116:16. Dr. deVries relied on an IV formulation reference (Broadhead) that she agreed showed hemolysis and phlebitis are distinct. Tr. 860:12-861:17. Dr. Chambers testified consistently with Dr. deVries and Broadhead that there is “no theoretical basis or proven basis”

linking hemolysis to phlebitis. Tr. 597:9-17. No one explained how to measure injection site hemolysis, or even how to measure phlebitis, in order to see if the new versus old formulation made any difference. The claim term thus creates a “zone of uncertainty” about how to determine infringement, so the ’802 patent claims are invalid as indefinite. *Nautilus*, 572 U.S. at 909-910.

C. Claims 1, 7, and 18 of the ’802 Patent Are Invalid For Lack of Enablement and Written Description of the “Injection Site Hemolysis” Limitation.

However Plaintiffs try to define injection site hemolysis, the patent still never substantiates any reduction. The patent never shows administering minocycline to anything or anyone, much less showing any reactions at an injection site. Tr. 596:21-597:5. The specification contained blood cell experiments on hemolysis testing, which showed reduced “hemolysis” generally, but never “injection site” hemolysis as the claims require. And even those blood cell experiments did not show any real-world impact because they did not use real-world conditions. As Dr. Chambers explained, a POSA could not interpret the *in vitro* studies from the ’802 patent as justifying any reduced hemolysis in subjects because they represent completely artificial conditions: the drug is highly concentrated, the drug is sitting stagnant in a pool of saline, and there is no natural blood flow or buffering effect. *See* Tr. 597:18-600:25 (explaining the shortcomings and lack of reliability for the patent’s *in vitro* tests). If Plaintiffs’ claim construction for “subject” is adopted, limiting the term to only humans, then the Section 112 concern is even more problematic because the patent lacks any human hemolysis data. In addition, the patent shows hemolysis is not reduced compared to another formulation “without magnesium” since calcium formulations had the same effect. Tr. 412:23-413:10 (Griffith). Thus, the asserted claims of the ’802 patent are also invalid for failing to meet the enablement and written description requirements under 35 U.S.C. § 112.

D. All Asserted Claims Are Invalid for Lack of Written Description and Enablement for the pH Limitations.

Claims 1 and 18 of the '802 patent all require the formulation to be an “aqueous solution” of minocycline where magnesium-to-minocycline ratios are “greater than about 4:1,” and stake out claims for the entire pH range 4-6. Asserted claim 27 of the '105 patent has an even broader pH range of 4-7. The specification “must enable one of ordinary skill in the art to practice the full scope of the claimed invention.” *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1243-1245 (Fed. Cir. 2003). To the contrary, the specification itself shows non-enablement. *Id.*

Dr. Klivanov explained why the specification did not justify the full scope of what Plaintiffs claimed. Tr. 526:2-527:14. In addition, Table 30 was discussed several times at trial, because that is where the patent shows a handful of tests to see if solutions could be made at various pH options. Table 30 shows a “binary end point, insoluble/soluble,” looking at whether minocycline did or did not form an aqueous solution. Tr. 885:17-24 (deVries). Claims 1 and 18 of the '802 patent and claim 27 of the '105 patent all include pH 6 within their range. Yet when looking at the data for pH 6, and in the row for “10 mg/ml minocycline,” the data shows that “0” or no magnesium added were soluble (open circles) whereas adding any amount of magnesium at all data points were insoluble (closed circles). Tr. 886:22-25. That 10 mg/ml is important because it is the same concentration used in Formulation 4, the example from the patent that Dr. deVries testified corresponded to the current commercial Minocin product. Tr. 205:1-9. Thus, Table 30 itself shows that using a claimed formulation would **not** work at pH 6, even though the claim **includes** pH 6. Making matters worse, Dr. deVries further testified that the patent showed “a wide range” of concentrations “between 1 and 50 milligrams per mil,” not just 10 mg/ml. Tr. 205:10-13. Yet Table 30 shows that for concentrations of 20 mg/ml and 30 mg/ml, the pH 6 results did not even show any data at all. Tr. 887:1-3. The situation is even worse for pH 7, as required by the

'105 patent, because no data was provided beyond 1 mg/ml. Tr.887:16-25. Table 30 by itself thus shows that “the specification clearly and strongly warns that such an embodiment” would not work, even though it is within the scope of the claims. *AK Steel*, 344 F.3d at 1244.

E. Claim 18 of the '802 Patent Is Invalid for Lack of Written Description and Enablement Because of the Claimed Volume Range.

Claim 18 of the '802 patent also fails the written description and full scope enablement requirements for the volume limitation. The claim requires the total volume of the “composition administered is less than 500 mL,” which includes the entire range 0-500. Tr. 614:6-14. Dr. Friedman conceded that a clinician would never use very low volumes because “that, one, would substantially affect the therapeutic effectiveness of the drug and, two, could be toxic to the patient.” Tr. 714:8-18. If the threshold is testing for effectiveness and toxicity, as Dr. Friedman testified, then that would require clinical trials for along the entire claimed volume range. Tr. 615:3-10. But the patent specification shows no clinical trials, or even administration of any volume to any patient. Tr. 614:6-615:2. The specification provides minocycline formulation examples using only one volume: 10 mL. Example 13, Formulations 1-4. Yet that volume, according to Plaintiffs' own experts, could not be administered as-is, even though it fits within the claimed “less than 500 mL” range. Tr. 276:13-16. Dr. deVries was happy to criticize the prior art for having “no actual data,” Tr. 810:9-15, so when it comes to the claimed volume range, Dr. Chambers pointed out “there's no data.” Tr. 614:15-20. Therefore, claim 18 of the '802 patent improperly stakes out the entire range from 0 mL to 500 mL, but the specification does not show the inventors possessed the whole range and does not enable one to practice this entire range.

F. Claim 27 of the '105 Patent Is Invalid for Lack of Written Description and Enablement Because of the Claimed Osmolality Range.

Claim 27 of the '105 patent fails the written description and full scope enablement requirements for the osmolality limitation. The claim requires the osmolality of the claimed

“composition” must be “less than about 500 mOsmol/kg,” which includes the entire range 0-500. Tr. 610:6-9. Whether that is construed to apply to the reconstituted vial or to the diluted IV bag, either way the specification does not justify the full scope of the claimed range. There are only two actual minocycline formulation osmolalities reported in the patent: 275-375 in Formulation 2 of Example 13, and 150-250 in Formulation 4 of Example 13. Tr. 833:13-19. Dr. Chambers explained that “the entire range is not safe” because very low osmolalities towards “zero” using the “example of water” causes “harmful effects.” Tr. 610:10-611:3. Dr. Friedman agreed that blood osmolality is “around 300 milliosmols per kilogram” and “to minimize the stress on the body, it is desirable to have the osmolality in the vicinity of this physiological osmolality range.” Tr. 470:4-8. Dr. Friedman further testified that “going too low risks the problem of tissue damage at the low end,” and although he asserted “a POSA would know that there is a lower limit,” he never stated what that was or where it was disclosed in the patent. Tr. 716:20-717:8. Therefore, claim 18 of the ’802 patent does not have written description and is not enabled for the entire range 0-500 mL.

Conclusion

For the above reasons, the Court should find Nexus is not liable for infringement, the patents are obvious, and are invalid under Section 112.

Dated: July 12, 2023

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**IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS**

MELINTA THERAPEUTICS, LLC,)	
MELINTA SUBSIDIARY CORP., and)	
REMPEX PHARMACEUTICALS, INC.,)	
)	
Plaintiffs,)	C.A. No. 1:21-cv-02636
)	
v.)	Judge John F. Kness
)	Magistrate Judge Maria Valdez
NEXUS PHARMACEUTICALS, INC.,)	
)	
Defendant.)	

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claimed composition itself was not obvious. *See Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306-07 (Fed. Cir. 2015).

V. DEFENDANT’S SECTION 112 ARGUMENTS ARE UNSUPPORTED AND CONCLUSORY

A. “Injection Site Hemolysis” Is Not Indefinite

Plaintiffs have already addressed Defendant’s indefiniteness argument regarding “injection site hemolysis.” (Plt. Br. at 7-12.) Defendant states that “Dr. Friedman never explained how to measure injection site hemolysis” (Def. Br. at 46), which is incorrect. Both Plaintiffs’ experts and Mr. Griffith discussed in detail the in vitro model and data disclosed in the specification describing how to measure hemolysis and compare formulations. That model was valid, well-known in the prior art, and accepted by FDA without any confusion regarding how to assess the hemolysis potential of a formulation. (FOF, ¶¶ 81, 84-85.) The fact that “hemolysis and phlebitis are distinct” (Def. Br. at 46) does not mean they are unrelated, and the specification makes clear phlebitis can result from hemolysis. (FOF, ¶¶ 65-67.) Defendant’s criticism comes down to the absence of an in vivo or clinical example in the specification, but Defendant does not cite any legal authority suggesting that is a requirement. (Def. Br. at 46-47.) There is no “zone of uncertainty.” Defendant clearly understood what injection site hemolysis is when it represented to FDA multiple times that magnesium in its ANDA product reduces hemolysis. (FOF, ¶ 113.) Defendant’s unsupported and conclusory assertions are not clear and convincing evidence to invalidate the patent.

B. “Injection Site Hemolysis” Does Not Lack Enablement or Written Description

Plaintiffs have already addressed Defendant’s enablement and written description arguments regarding “injection site hemolysis,” including Dr. Chambers’ specific criticisms of

the in vitro hemolysis model. (Def. Br. at 47; Plt. Br. at 7-12, 43.) Defendant’s criticism again comes down to the absence of an in vivo or clinical example in the specification, but again Defendant does not cite any legal authority.

Defendant vaguely refers to the minocycline-calcium formulations in the specification but does not explain how they are relevant to whether the specification adequately enables and describes the claimed minocycline-magnesium formulations. (Def. Br. at 47.) The patent includes data demonstrating that the claimed minocycline-magnesium composition reduced hemolysis compared to the minocycline formulation without magnesium or any other metal cation. (FOF, ¶¶ 74-78.) The specification makes clear that the inventors compared minocycline formulations containing either “Mg²⁺ or Ca²⁺” to the control formulation without any metal cations. (FOF, ¶ 72.) How minocycline-magnesium formulations compare to minocycline-calcium formulations is irrelevant to enablement of the claimed minocycline-magnesium formulations. Defendant seems to imply that the claimed minocycline-magnesium composition must have reduced hemolysis compared to *any* “composition that does not include magnesium”—which is absurdly literal and would include comparing the claimed composition to compositions without minocycline at all, which makes no sense.

C. The pH Limitations Do Not Lack Enablement or Written Description

Plaintiffs already addressed Defendant’s enablement and written description arguments regarding the pH limitations, specifically the assertion that the claimed invention does not work at pH 6. (Def. Br. at 48-49; Plt. Br. at 42-43.) There is no requirement that the claimed invention work at pH 6 *for each possible concentration*. Concentration is not a separate claim limitation, and the specification makes clear that the concentration of the claimed composition can be varied across a wide range. (FOF, ¶ 226.) Table 30 and the stated conclusion in the

specification show that the claimed composition works at pH 6 at for example concentrations of 1 mg/mL and 5 mg/mL, and for pH 7 at for example 1 mg/mL. (FOF, ¶¶ 250; *see also* 224-225.) Thus, for any pH within the claimed pH ranges, there are concentrations at which the claimed composition is soluble. (FOF, ¶ 226.) Defendant has not shown any pH at which the claimed invention does not work, let alone a sufficient number of inoperable embodiments to meet the legal standard. *See Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1188-90 (Fed. Cir. 2014); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984). Defendant points to Formulation 4 of Example 13, which is the claimed composition with 10 mg/mL concentration and 5:1 molar ratio. (Def. Br. at 48.) The specification makes clear that formulation works (“suitable for intravenous administration”) at pH 4.5-5.5. (PTX-001 at 38:33-43.) Nothing requires the patent to show *that formulation* also works at pH 6.

D. The Volume and Osmolality Limitations Do Not Lack Enablement or Written Description

Plaintiffs have already addressed Defendant’s enablement and written description argument regarding the volume and osmolality limitations. (Def. Br. at 49-50; Plt. Br. at 44-45.)

Defendant states that the “specification provides minocycline formulation examples using only one volume: 10 mL” (Def. Br. at 49) which Defendant wrongly asserts is the administration volume. 10 mL in the examples is the reconstitution volume of the compositions, not the total volume for administration referred to in Claim 18 of the ’802 patent. (FOF, ¶ 251.) The specification discusses the process of diluting the reconstituted composition to form an admixture and includes the label for the prior art intravenous minocycline product, which describes the different volumes for reconstitution and further dilution. (FOF, ¶¶ 51-52, 71.)

July 26, 2023

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**IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS**

MELINTA THERAPEUTICS, LLC,
MELINTA SUBSIDIARY CORP., and
REMPEX PHARMACEUTICALS, INC.,

Plaintiffs,

V.

NEXUS PHARMACEUTICALS, INC.,

Defendant.

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) C.A. No. 1:21-cv-02636
)
) Judge John F. Kness
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) Magistrate Judge Maria Valdez
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NEXUS PHARMACEUTICALS, INC.'S RESPONSIVE POST-TRIAL BRIEF

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Plaintiffs rely on assertion and conclusions, rather than actual evidence. Plaintiffs failed to meet their burden on direct infringement, because they never did the right tests, even though they had every opportunity to do so. Plaintiffs failed on indirect infringement, because they concede Nexus's label does not mention osmolality or injection site hemolysis, and wrongly assert these should be ignored for purposes of inducement or contributory infringement. Meanwhile for invalidity, Dr. Klivanov walked through documents and chemistry in great detail to show the express prior art trail that rendered the asserted claims obvious. Dr. Friedman and Dr. deVries admitted so many facts on cross examination that Plaintiffs' invalidity rebuttal shattered. Judgment should be entered in Nexus's favor, so that its generic can finally be marketed.

I. PLAINTIFFS' CLAIM CONSTRUCTION SHOULD BE REJECTED

Plaintiffs disregarded the parties' agreement that "no claim terms required construction by the Court" and thrust claim construction issues anyway into the trial, forcing trial objections on the first day. D.I. 250 at 5. Plaintiffs' belated claim construction arguments should be rejected.¹

A. Plaintiffs' "Composition" Construction Is Contrary To The Intrinsic Evidence

Plaintiffs focus on the meaning of "composition" only in the "asserted claims," but other claims in the same patent are "valuable sources of enlightenment as to the meaning of a claim term." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005). For example, claims 21-23 of the '802 patent require that the "**composition is administered** in less than" 60, 40, or 20 minutes. PTX 1 at 42:3-8. Plaintiffs argue the "composition" is the reconstituted product (D.I. 249 at 3), but that would render claims 20-23 meaningless because parties agree the reconstituted vial cannot be administered at all. *See Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321 (Fed. Cir. 2007) (affirming construction that avoided rendering ratios in dependent

¹ Plaintiffs did not argue that the term "subject" is limited to "human," and waived that issue. Therefore, the Court should adopt Nexus's proposed construction. D.I. 250 at 9.

claims meaningless). Plaintiffs' experts even admitted dependent claims relating to administering a certain volume of the "composition" (e.g., asserted claim 18 of the '802 patent) must refer to what is actually administered and not the reconstituted product for this reason. D.I. 250 at 7. Because a claim term must be construed consistently throughout all the claims, *see CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1159 (Fed. Cir. 1997), "composition" in claim 1, like in the dependent claims, must mean the composition is what is administered.

The specification describes many different examples of "compositions" without a singular definition, and includes administered compositions. Plaintiffs ignore those statements where the "composition" is *administered* intravenously, to treat bacterial infections, at certain volumes, or for certain time periods. PTX 1 at 6:26-41. None of these "administrations" would make sense if the "composition" is a reconstituted vial. The disclosures regarding methods of treatment are also consistent with Nexus's construction. PTX 1 at 19:15-20, 39-58. The specifications and the claim language thus consistently confirm "composition" is the administered formulation.

Plaintiffs try to avoid the proper construction of "composition" by back-dooring an argument about the word "administering." But as Nexus showed in its opening brief, the plain and ordinary meaning of "administering" is a one-step action and is not the two-step process of diluting and then administering. D.I. 250 at 6-7. Dr. Friedman agreed, testifying that the reconstituted solution is mixed with a diluent, "which will then be provided for intravenous administration...." Tr. 102:12-23. Plaintiffs' brief also supports Nexus's position, citing to the specifications' statement that "[o]nce admixed, the tetracycline solution is ready for administration by or to the patient." D.I. 249 at 4 (*quoting* PTX 1 at 13:53-54). This word choice shows the patents clearly considered admixing a separate step from administering, which just means "giving."

Plaintiffs also rely on irrelevant extrinsic evidence including the parties' product labeling,

but extrinsic evidence cannot contradict the clear intrinsic evidence. *Immunex Corp. v. Sanofi-Aventis U.S. LLC*, 977 F.3d 1212, 1222 (Fed. Cir. 2020). Plaintiffs assert that the pH of the examples must limit the claims, but that is wrong because claims are not limited by the specification, and because the patent examples do not say the 10 mL formulations should not be administered. *See Myco Indus., Inc. v. BlephEx, LLC*, 955 F. 3d 1, 14 (Fed. Cir. 2020). Moreover, while the product labels report the pH of the reconstituted formula, they did not exist at the time of the patent, and Plaintiffs ignore the “Administration” section which also discloses the pH of the diluted composition that is actually administered. PTX 31 at NEXUS-MIN-0001812; PTX 130 at MELINTA017504; *see also* Tr. 272:24-273:2 (deVries).

B. Plaintiffs Do Not Support Their Construction For “Injection Site Hemolysis”

The term “injection site hemolysis” is indefinite as Nexus showed in its opening brief (D.I. 250 at 46-47) and below. Plaintiffs’ proposed construction of the term has several other flaws. First, Plaintiffs’ arguments (D.I. 249 at 7-10) relate to hemolysis and not *injection site* hemolysis, which is an undefined term not discussed in any intrinsic or extrinsic evidence. D.I. 250 at 46-47. Second, Plaintiffs rely on statements by Nexus’s corporate representative regarding injection site hemolysis, but she never defined that term, much less explained how to measure it relative to anything else. Tawde Dep. 97:20-98:03. Therefore, the statements are irrelevant to claim construction and do not shed light on what the claim term means.

Plaintiffs also gloss over the dispute they created regarding the meaning of “does not include magnesium” that defines the comparator in the ’802 patent. The patentee chose to use those words and “[c]ourts do not rewrite claims; instead we give effect to the terms chosen by the patentee.” *K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1364 (Fed. Cir. 1999). Plaintiffs’ attempt to tack on the extraneous “or other metal cation” language is improper because that is a separate term in the specification: “[w]here the specification does not *require* a limitation, that limitation should

not be read from the specification into the claims.” *E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430, 1433 (Fed. Cir. 1988) (emphasis in original) (internal quotation omitted). The specification did not define “does not include magnesium” as “no metal cation,” and instead identified several cations and Plaintiffs chose in the claim to exclude only one, magnesium.

II. PLAINTIFFS HAVE FAILED TO PROVE INFRINGEMENT

A. Plaintiffs Failed to Prove Direct Infringement

Plaintiffs’ infringement allegations depend on unsubstantiated inferences and assumptions, about both injection site hemolysis and osmolality. Plaintiffs did not do the tests to show direct infringement. Instead of demonstrating Nexus’s knowledge and specific intent to infringe those two essential claim terms, Plaintiffs relied on the flawed legal claim that simply telling people to use minocycline to treat bacterial infections is enough.

1. Plaintiffs Failed to Prove Osmolality (’105 Patent)

Plaintiffs did not meet their burden to show that Nexus’s product will meet the claimed osmolality limitation, and even mix and match between evidence and competing claim constructions to try to cobble together a position. Plaintiffs’ efforts fail under any construction.

If the Court rules “composition” for the ’105 patent is the reconstituted product only, then the product at issue is the Nexus vial when 5 mg/mL water is added. Plaintiffs’ infringement evidence, however, focused on products reconstituted at 10 mg/mL, which adjusted for 5 mg/mL showed values above 500 mOsmol/kg according to Dr. deVries’s proposed assumptions. D.I. 249 at 23; D.I. 250 at 13. In other words, Plaintiffs’ own data shows Nexus’s product will not infringe under their construction. Plaintiffs refer to osmolality data in “the patents-in-suit,” *id.*, but those examples are also only for 10 mg/mL solutions, not 5 mg/mL. Plaintiffs then resort to the argument that an osmolality “can also be calculated,” *id.*, but Plaintiffs opted not to do any.

If “composition” is the administered IV bag as Nexus has shown, then the relevant product

is the Nexus product when diluted in 100-1000 mL of water. For that product, Plaintiffs have no testing at all. Instead, Plaintiffs rely only on “standard diluents” with osmolality “less than 500” and conclude the “infusion admixture must also have an osmolality less than 500.” D.I. 249 at 23. But there is no basis, evidentiary or otherwise, for this assertion. Plaintiffs turn to Nexus’s invalidity position about the “standard of care,” but as Nexus pointed out in the opening brief, standard of care helps show a value is obvious but is not itself proof that Nexus’s formulation meets the claimed 500 mOsmol/kg threshold. D.I. 250 at 15.

Under either circumstance, Plaintiffs failed to prove direct infringement of the osmolality limitation. Since Plaintiffs did no tests or calculations, Plaintiffs now assert instead of any proof that osmolality is merely an inherent property, and is “necessarily” under 500 mOsmol/kg for all formulations: old and current; vial and IV solution. D.I. 249 at 23. Admitting to inherency is a serious concession, because if the court accepts Plaintiffs’ inherency argument for *direct* infringement, Nexus does not have to separately prove it for *obviousness*. And either way, Plaintiffs still have to separately show *indirect* infringement, as discussed below.

2. Plaintiffs Disregard the “Consists Of” Claim Term (’802 Patent)

Plaintiffs never separately address the “consisting of” problem with the claims in the ’802 patent, since those all require administering only the ingredients in the claim and no other ingredients. In fact, if Nexus’s construction is accepted, then Plaintiffs concede that “it is undisputed that the reconstituted solution of minocycline is never directly administered.” D.I. 249 at 6. But that is what the claims require in view of Plaintiffs’ choice to use “consisting of” claiming.

3. Plaintiffs Failed to Prove Reduced Injection Site Hemolysis (’802 Patent)

Plaintiffs did not prove the reduced injection site hemolysis claim limitation. Despite Plaintiffs’ bold heading regarding “substantial real-world clinical evidence,” they present nothing more than Dr. Friedman’s anecdotal assertions. D.I. 249 at 19-22. No one ever compared clinical

evidence using the old and current Minocin IV products, nor could they, “because they were not available simultaneously.” Tr. 684:24-685:4. In fact, Dr. Friedman had no real support; not even one of his own 300+ articles mentioned the supposed problem or the supposed benefit. Tr. 184:9-12, 753:9-20. Despite Plaintiffs’ claim, Dr. Chambers did rebut these and other points. D.I. 250 at 17-20. Dr. Friedman’s vague references to general “tolerability” issues (phlebitis and thrombophlebitis) are not the claimed injection site hemolysis. Dr. Chambers testified hemolysis is *not* phlebitis or thrombophlebitis and “there is no theoretical basis or proven basis that those are linked, pathophysiologically.” Tr. 597:9-17. Even Dr. deVries admitted “phlebitis refers to inflammation of the vein wall,” which is “different” than hemolysis because “a red blood cell is not in the vein wall.” Tr. 860:12-20. Plaintiffs could have compared the old and current formulations and tested for “free hemoglobin” as Dr. Chambers and the prior art Broadhead reference recommended. Tr. 600:18-25; PTX 225 at MELINTA017621. They did not.

Plaintiffs’ bullet-point list of testing data, D.I. 249 at 8, has one glaring omission that Plaintiffs simply ignore: three *in vivo* rabbit ear tests that all showed no difference between formulations with and without magnesium.² DTX-0041_0007; Tr. 865:18-868:13. Those three tests are critical because they are the only ones that tested venous tolerance using actual conditions of a blood vessel, as opposed to artificial conditions with a stagnant pool of blood cells, no buffer, and long exposure time to minocycline. Tr. 597:21-600:1 (Chambers). Plaintiffs’ Harrigan reference confirms what Dr. Chambers explained, that “human blood is a natural buffering agent.” PTX 175 at MELINTA017602. Plaintiffs’ Broadhead reference also confirms that real-flow

² Plaintiffs list one allegedly “in vivo” test, but that was a “subcutaneous injection of the drug directly to the rear flank of the mouse” and “not an infusion” (not IV), and also did not even test for hemolysis (damage to blood cells) but instead “damage to dermal cells.” Tr. 409:15-410:5

conditions are necessary to test hemolysis comparisons because stagnant conditions are artificial and exposure time is “critical.” PTX 225 at MELINTA017621; Tr. 858:9-860:8. Plaintiffs rely on Hoover 1990 to justify their *in vitro* tests, but that reference used different conditions (whole blood—including its natural buffers—versus Plaintiffs’ test that isolated red blood cells). PTX 177 at MELINTA015893. More critically, Hoover used *in vivo* rabbit ear studies as the gold standard for testing, *id.* at MELINTA015892, which is the very testing Plaintiffs ignored.³

Plaintiffs also never properly applied the claim term itself, comparing reduced injection site hemolysis between the claimed formulation and a formulation that “does not include magnesium.” Under Plaintiffs’ construction for that term, none of Plaintiffs’ tests—even their *in vitro* tests—used the same formulation that differed only by adding magnesium. They had several pertinent differences including pH, concentration, or an added base. Tr. 280:8-281:9; 287:21-288:21 (deVries). If Nexus’s construction is applied, then the patent specification itself shows this limitation is not met because it reports that the claimed magnesium-containing formulation did not reduce hemolysis compared to a calcium-containing formulation. Tr. 412:23-413:10 (Griffith).

Lacking any testing proof, Plaintiffs next assert in the alternative that the higher pH and lower volume options in the current label must mean reduced injection site hemolysis. D.I. 249 at 20. But there is no such connection. Tr. 584:18-22 (Chambers). If it were as simple as citing higher pH and lower volume to equate them to reduced injection site hemolysis, FDA did not agree. PTX 88 at 4. As Dr. deVries admitted, just changing the pH and volume did not justify a claim to improved tolerability, because “if you want to make a claim about a clinical difference, you have to do a clinical trial.” Tr. 250:24-251:10.

³ Hoover 1990 also was not about minocycline, and never mentioned it, so it is telling that Plaintiffs conveniently refer to any tetracycline-class reference when they see fit.

Plaintiffs allege Nexus’s FDA submissions referencing “hemolysis reduction” and Dr. Tawde’s testimony about the same are “unrebutted admissions.” D.I. 249 at 17-18. But **Dr. Tawde herself** rebutted the comments in her testimony, explaining the FDA submission was “based upon the literature” and “Nexus did not perform any studies to confirm the function of magnesium.” Tawde 87:10-92:12. Nexus never tested for hemolysis, much less injection site hemolysis, or compared any two formulations to one another. Tawde 97:20-98:03. FDA required Nexus’s formulation to have that the same ingredients as Plaintiffs (Tr. 205:21-206:18), but FDA never made any finding about magnesium’s function nor asked Nexus to test for hemolysis reduction. We know FDA never accepted magnesium as a hemolysis reducer because it required proof from Plaintiffs before allowing such a claim, DTX-0131_0006, and because Plaintiffs in their own FDA submission called magnesium a “solubilizer/stabilizer.” DTX-0057; Tr. 395:21-24 (Griffith). The *Intendis* case is irrelevant because that case involved infringement under the “doctrine of equivalents,” not asserted here, which has a separate “function” test not applicable here. *Intendis GmbH v. Glenmark Pharms. Inc.*, 822 F.3d 1355, 1362 (Fed. Cir. 2016).

Left with no other actual proof of direct infringement, Plaintiffs again assume reduced injection site hemolysis exists as an inherent property because they cannot prove it with any evidence. D.I. 249 at 17. That concession makes the reduced hemolysis claim limitation irrelevant for invalidity purposes, even though that was touted as a supposed benefit for the ’802 patent.

B. Plaintiffs Failed to Prove Contributory Infringement

Plaintiffs all but abandoned contributory infringement in their brief. Plaintiffs have the burden to prove—in addition to direct infringement—that Nexus knew of infringement, that its product was “especially made or especially adapted” for infringing, and with no “substantial noninfringing use.” 35 U.S.C. § 271(c). They offer one throwaway paragraph, and it fails to prove any of those required criteria. D.I. 249 at 27. For Nexus’s knowledge of infringement, Plaintiffs

look to only one claim limitation, “to treat bacterial infections” and stop there. *Id.* That is woefully incomplete. Plaintiffs incorporate by reference Section IV.B of their brief, but that section compares two products to each other, and does not even mention osmolality. *Id.* at 14-15. Since Plaintiff shirked any claim-by-claim analysis, they also ignored the admitted substantial non-infringing uses. For the ’105 patent, Plaintiffs never disputed that for the D5W/Saline combination allowed by Nexus’s label, the osmolality for the IV bag diluent itself even before adding drug is over 500 mOsmol/kg. Tr. 654:21-25, 681:9-13. For the ’802 patent, in addition to the injection site hemolysis issue, claim 7 requires pH 4.5-5.5, but Dr. deVries admitted that the Nexus label for administered formulation allows the non-infringing pH 6.0. Tr. 272:24-273:23. Claim 18 requires volume less than 500 mL but Dr. deVries admitted that Nexus’s label allows non-infringing volumes above 500 mL. Tr. 273:24-274:10, 247:24-275:7.

C. Plaintiffs Failed To Prove Inducement

On inducement to infringe, instead of pointing to any factual dispute, Plaintiffs concede that neither hemolysis nor osmolality are on Nexus’s label. The dispute is therefore a legal one: does the label need to say anything about these claim elements in order to show inducement? The answer is yes, because of consistent Federal Circuit case law requiring an accused infringer to induce infringing conduct. That means the label and the patent claims must match. Plaintiffs contradict Federal Circuit law and trot out already-rejected legal theories.

To hold a defendant liable for a third party’s patent infringement, the defendant’s label “must encourage, recommend, or promote infringement.” *Takeda Pharms. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). Despite the exact quote, Plaintiffs call Dr. Chambers’s opinion “incorrect” for considering whether “Nexus’s label will instruct, teach, or suggest infringement.” D.I. 249 at 24. Mere knowledge that someone may infringe, or that the product may infringe once administered, is not enough to show inducement: “The accused

infringer must have ‘knowingly aided and abetted’ direct infringement.” *Takeda*, 785 F.3d at 630 (citing *Warner-Lambert*, 316 F.3d at 1363). Without a clear link to the label, relying on physician understandings or Nexus internal documents “would seem to too easily transform” into induced infringement the legally irrelevant “mere knowledge of infringing uses.” *Takeda*, 785 F.3d at 632.

Plaintiffs confuse *acts* that they say will result in direct infringement—administering minocycline to treat bacterial infections—with *inducing patent infringement* (which also requires reduced injection site hemolysis and certain osmolality levels). When presented with this exact question, the Federal Circuit already answered it in Nexus’s favor. In *DSU Medical Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1305 (Fed. Cir. 2006), the court addressed “whether the purported infringer must intend to induce the infringement or whether the purported infringer must merely intend to engage in the acts that induce the infringement.” The Federal Circuit held “inducement requires evidence of culpable conduct, directed to encouraging another’s infringement, not merely that the inducer had knowledge of the direct infringer’s activities.” *Id.* at 1306. The “culpable conduct” means “affirmative intent to cause direct infringement.” *Id.* Far short of culpable conduct, Nexus’s label is indifferent to whether any physician cares to reduce injection site hemolysis or to use any particular osmolality. Nexus does not have specific intent to infringe, so it cannot be liable.

In *Bayer*, the court rejected on a Rule 12(c) motion to dismiss the same argument Plaintiffs make here, that “other effects ‘that do not treat a disease or condition’” need not be on the label. *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1323 (Fed. Cir. 2012). In *Bayer*, the FDA-approved labels for both the patentee and the accused infringer were labeled for “oral contraception” (also known as a “gestagenic effect”), whereas the claims required that **and** “anti-androgenic effect and antialdosterone effect.” *Id.* at 1319-20. The parties did not dispute all three effects did occur. In fact, Bayer could even point to claim terms on the label itself, but just not in

the “Indications and Usage section of the FDA-approved label.” *Id.* Nonetheless, the Federal Circuit held *even with* the reference to claim terms in other places on the label, “the fact that certain of the effects of a drug are described in the Clinical Pharmacology section of the label does not mean that the FDA has approved the use of the drug to produce those effects.” *Id.* Here, Plaintiffs concede that reduced injection site hemolysis and osmolality are not anywhere on the label.

Plaintiffs had the real-world opportunity to change the old Minocin IV label to claim improved tolerability. Plaintiffs asked FDA to change the label to show improved tolerability, but FDA refused, requiring additional proof in the form of full clinical trials. PTX 88 at 4; Tr. 601:3-12 (Chambers); 863:12-864:9 (deVries). Plaintiffs chose not to do them. *Id.* So Plaintiffs’ experts understood that adverse events had to “stay[] in the label.” Tr. 178:24-179:15; 251:11-19; 253:20-254:1. Plaintiffs bought the old Minocin IV and reported to FDA that it was “acquired,” so any clinical trials were “considered no longer necessary.” DTX-0072_006. Plaintiffs therefore cannot make any claims about reduced injection site hemolysis. Similarly, Nexus—who uses the same label—cannot make any such claims either, and therefore cannot and will not induce patent infringement. In fact, the current Minocin IV label—and Nexus’s label—contain all of the same warnings as the old Minocin IV label, and only add more regarding magnesium. Tr. 582:11-12. For osmolality, Plaintiffs never even tried to add it to the label, and they presented no evidence that anything stopped them from doing so, just like the label changes they made to pH and volume.

Plaintiffs attempt to distinguish Nexus’s several Federal Circuit cases where the label does not match the claim, arguing those cases relate to “a non-patented therapeutic use of the drug” that is “different from the use or indication to which the method of treatment patent claims are directed.” D.I. 249 at 26. That is the same here: the method of treatment patents relate to treatments directed to reduced injection site hemolysis and certain osmolality, whereas Nexus’s label is only

directed to treating bacterial infections. Nexus never added to its label or sought any approval for reduced injection site hemolysis or osmolality. Like the other cases Nexus cited, *Warner-Lambert* stands for the general proposition that infringement in pharmaceutical cases is “limited to an analysis of whether what the generic drug maker is requesting authorization for in the ANDA would be an act of infringement if performed.” *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364-65 (Fed. Cir. 2003). Plaintiffs decided to claim their alleged invention in a particular way with particular features, and cannot now ignore some of the claim limitations. Plaintiffs do not own a patent on merely treating bacterial infections alone. Just as in *Bayer*, “[Plaintiff] does not enjoy patent protection for the drug Yasmin or for the use of the drug for contraception alone”—the claims referred to additional effects. *Bayer*, 676 F.3d at 1320.

Plaintiffs see the weakness, and therefore add the alternative argument that this Court should “consider evidence beyond the ANDA label’s four corners” to prove intent. D.I. 249 at 24-25. But the cases they cite are far afield. In *GlaxoSmithKline*, intent was based on statements after sales began, communicated directly to physicians that went beyond the label and financial marketing models showing infringing market usage. *GlaxoSmithKline LLC v. Teva Pharms. USA, Inc.*, 7 F.4th 1320, 1335 (Fed. Cir. 2021). None of that is applicable here. The *Abbott Labs* case is not even an indirect infringement case, as there the Federal Circuit **reversed** the finding of direct infringement. *Abbott Lab’ys v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). The *AstraZeneca* citation is just as egregious: the opinion does contain the words “specific intent finding was not based solely on the proposed label,” but the case is about the words on the label itself, plus defendant’s awareness “that the label presented infringement problems.” *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060-61 (Fed. Cir. 2010). There is no such issue here.

Plaintiffs also include district court cases that are not only non-binding, but different. Plaintiffs strangely cite to *Sanofi*, but infringement was still based on the label, and the only question was whether the label had to “limit a drug only to a specific use in order to induce infringement,” or could more generally “encourage some physicians to prescribe dronedarone to patients with risk factors.” *Sanofi v. Glenmark Pharm. Inc., USA*, 204 F.Supp.3d 665, 679-680 (D. Del. 2016). When the Federal Circuit addressed this very same case on appeal, it emphasized the label-based rule: the patent claim for “decreasing a risk of CV hospitalization” was expressly met by the label indication “to reduce the risk of hospitalization for atrial fibrillation.” *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 642-643 (Fed. Cir. 2017). Finally, in *Bone Care*—decided before the benefit of *Takeda*—the district court expressly ruled that “defendants’ proposed product labels would infringe each element” by “instructing users to perform each element of this claim.” *Bone Care Int’l LLC v. Roxane Labs. Inc.*, No. 09-cv-285, 2012 WL 2126896, at *31 (D. Del. June 11, 2012). The patentee in *Bone Care* also presented substantial evidence that Plaintiffs here could not including “clinical trials” and “literature” that proved the claimed effect would occur. *Id.*

Plaintiffs go so far as to assert that courts find administration alone to be sufficient for infringement “even if the label does not explicitly state [claimed] properties.” D.I. 249 at 25-26. Plaintiffs do not explain how any of the cases they cite reach such a conclusion, and ***all four of them are once again district court cases*** that do not apply and address other facts. *Bone Care* was addressed above, and confirmed that “mere knowledge of possible inducement does not constitute inducement.” *Bone Care*, 2012 WL 2126896, at *10. *Orexigen* only said that the “patient” did not have to know the tablets met all of the claimed steps—it never excused Plaintiff from proving what the defendant intended through the label. *Orexigen Therapeutics, Inc. v. Actavis Labs, FL Inc.*, 282 F.Supp.3d 793, 816 (D. Del. 2017). *Cephalon* focused on an impurity level in the formulation

if it had been stored for three months, which “does not require action to infringe” whereas the claims here are all required administering the formulation with the claimed osmolality and to achieve reduced injection site hemolysis. *Cephalon, Inc. v. Slayback Pharma LLC*, 456 F.Supp.3d 594, 625-626 (D. Del. 2020). Plaintiffs cite *Ferring Pharms. Inc. v. Fresenius Kabi USA, LLC*, 2022 WL 17584954, at *34-*35 (D. Del. 2022), and even though the court found that the claimed feature did not have to be on the label for two of the asserted patents, the court found both patents invalid as obvious because they claimed mere inherent properties. *Id.* at *40-*41. If administration alone were sufficient to show infringement, then the same must be true for invalidity: the test is the same for infringement and invalidity. *See, e.g., Upsher-Smith Labs, Inc. v. PAMLAB, LLC*, 412 F.3d 1319, 1322 (Fed. Cir. 2005) (“A century-old axiom of patent law holds that a product “which would literally infringe if later in time anticipates if earlier.”).

Plaintiffs make the second alternative argument that even though there is no encouragement on Nexus’s label, following the label instructions would “inevitably lead some physicians to infringe,” which is yet another misreading of the case law. D.I. 249 at 25. Each case required patent claim language on the label. In *Eli Lilly*, the Federal Circuit found “unambiguous” express “repeated instructions” matching the patent claims, which would “inevitability” lead some to infringe, even if others would “ignore” the label. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1368-69 (Fed. Cir. 2017). The *Sanofi* district court decision applied the same proposition: a label must still encourage infringement, though there is no requirement “that a label expressly limit a drug only to a specific use in order to induce infringement.” *Sanofi*, 204 F. Supp. 3d at 680. Plaintiffs also again cite *AstraZeneca*, but the court again considered “whether the proposed label instructs users to perform the patented method.” *AstraZeneca*, 633 F.3d at 1060. The *AstraZeneca* Court referred to “inevitable” infringement because the label did not expressly

state “once per day”—which is what the patent required—but the label expressly did say to start with two doses and then “downward-titrate to the lowest effective dose,” which necessarily meant the same thing as using one dose per day. 633 F.3d at 1048, 1057; *see also Takeda* 785 F.3d at 634 (discussing *AstraZeneca*). No such facts are present here, showing that Plaintiffs are just quoting catch phrases from the cases, while ignoring their facts and holdings.

Finally, Plaintiffs’ third alternative argument is that “physicians will know and understand from reading the information in Defendant’s label that the products will infringe.” D.I. 249 at 27. But physicians’ independent knowledge or conclusions they draw are irrelevant to inducement because the point of inducement is whether *Nexus* made any instruction to encourage infringement. Plaintiffs are asking this Court to “look outside the label to understand the alleged implicit encouragement in the label, even while it admits that evidence of mere knowledge of infringing uses is not sufficient.” *Takeda*, 785 F.3d 634. Plaintiffs wrongly assert that *Sanofi* affirmed inducement “even were claim term was not in label,” D.I. 249 at 27, whereas the Federal Circuit actually found that the clinical trials section of the label “identifies a class of patients as having been shown to achieve reduced hospitalization” that matched “the patent-claimed risk factors.” *Sanofi*, 875 F.3d at 645. Plaintiffs cite a footnote from the *Tyco* district court case, but its relevance is difficult to discern: the district court denied summary judgment because of an issue of fact regarding the defendant’s specific intent. *Tyco Healthcare Grp. LP v. Biolitec, Inc.*, No. C-08-3129 MMC, 2010 WL 3324893, at *6 & n.8 (N.D. Cal. Aug. 23, 2010). Plaintiffs cite *Lifetime* without explanation, which must have been a mistake, as the pages they cite do not refer to inducement and later pages that refer to inducement refer only to a pleading standard for alleging inducement. *Lifetime Indus., Inc. v. Trim-Lok, Inc.*, 869 F.3d 1372, 1377-78, 1380 (Fed. Cir. 2017).

III. PLAINTIFFS FAIL TO CHALLENGE OBVIOUSNESS

As shown in *Nexus*’s opening brief, the claims are obvious based on the old Minocin IV

label, CN'268, and Gibbs. D.I. 250 at § IV. Those provided the POSA a prior art pathway.

A. Plaintiffs' Criticisms of Obviousness Are Baseless

As a legal matter, “obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Nexus merely has to show a POSA would have *reasonably expected* to achieve the claims based on the prior art; “absolute predictability” is not needed. *Medichem, S.A. v. Rolabe, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). Plaintiffs’ claim that Nexus’s burden of proving invalidity here is “especially difficult” because two references were before the Examiner (D.I. 249 at 38) is wrong both legally and factually. Any supposed “enhanced burden” does not raise the burden of proof, even where the Patent Office assessed the same argument. *See Intercontinental Great Brands LLC v. Kellogg N.A. Co.*, 869 F.3d 1336, 1350-51 (2017) (affirming summary judgment of invalidity over considered art). But CN'268 was *not* before the Patent Office, and expressly taught magnesium would achieve the characteristics Plaintiffs’ experts admit would benefit the old Minocin IV product. Tr. 511:20-512:1 (Klibanov); 846:5-10 (deVries). The Patent Office also never expressly considered Gibbs by discussing it in a rejection. As a result, the burden in this case “may be more easily carried.” *SIBIA Neurosciences, Inc. v. Cadus Pharms. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000).

1. Plaintiffs’ Claims That a POSA Would Not Extrapolate from Doxycycline Formulations Are Illogical and Have Already Been Debunked by the PTO

Plaintiffs’ claim that a POSA would not look to doxycycline formulations in modifying formulations of the highly similar minocycline contradicts science, the prior art, and the Patent Office. As Dr. Klibanov explained at trial, a POSA would readily look to prior art formulations of other tetracyclines due to the known commonalities, even though they are of course not identical compounds. Tr. 475:1-16. Dr. Chambers said the same. Tr. 682:22-683:19. The law on

obviousness is clear: “if a technique has been used to improve one [compound], and a [POSA] would recognize that it would improve similar [compounds] in the same way, using the technique is obvious.” *KSR Int’l. Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

In fact, that is exactly what POSAs actually did in the prior art. As Dr. Klivanov explained, Gibbs used minocycline and doxycycline formulations in an essentially interchangeable manner, especially with respect to interaction with magnesium. Tr. 491:21-492:4. Tellingly, even Dr. deVries did exactly what she claims a POSA would not do. Her minocycline-related deVries 2006 application was based on an earlier patent that focused only on doxycycline, which had a nearly identical “detailed description of the invention.” *Compare* PTX 134 (deVries 2006) at [0016]-[0069] *with* DTX-0360 (deVries doxycycline patent) at 2:58-7:15). Dr. deVries admitted she relied on her prior doxycycline formulation experience for the minocycline project development, and that the two sets of formulations “seem similar.” Tr. 883:4-7; 882:12-22. Dr. deVries even agreed that the formulations only had to be “adjusted” because they were different compounds. Tr. 879:23-880:2. That is exactly what a POSA would do, since a POSA is not a cut-and-paste machine but rather a person of “ordinary creativity,” so minor tweaking is nothing more than a matter of routine experimentation. *KSR*, 550 U.S. at 421. Dr. deVries admitted that a POSA would easily know how to address such differences, such as varying the magnesium to minocycline molar ratio to assess characteristics such as solubility. Tr. 889:2-9.

For her application, Dr. deVries made the same argument she made in court to the Patent Office, but the Patent Office rejected it. Tr. 499:5-500:13 (discussing DDX2018, DTX-0038_0009, DTX-0037_0002). Dr. deVries had argued prior art should be ignored because they were not about minocycline specifically and instead disclosed other tetracyclines, but the PTO rejected that argument as “not [] persuasive” because of the shared “core structure and

characteristics” of minocycline “with the other species in the tetracycline genus.” *Id.* Dr. deVries never challenged this rejection that applied formulation approaches from another tetracycline to minocycline, and never explained at trial why she was making the same rejected argument.

Plaintiffs’ claim that Defendants’ experts “failed to address” differences between the two molecules is clearly false. D.I. 249 at 41. Dr. Klivanov clearly explained in great detail and citing significant supporting evidence why the doxycycline references were highly relevant and instructive here even though the compounds are not identical. *E.g.* Tr. 475:1-14, 495:3-21, 497:8-18; *see also* D.I. 250 at § IV.D.1. So, too, did Dr. Chambers. Tr. 682:22-683:19. Plaintiffs’ reliance on generalized comments that two different compounds are different are as irrelevant as they are tautological: they have nothing to do with magnesium-tetracycline formulations, and they never explain *why* any alleged differences would affect formulation. *See* D.I. 249. at 42. Plaintiffs had no response to the fact that magnesium was known to interact on the bottom half of the chemical structure, identical for minocycline and doxycycline. Tr. 899:20-900:10.

2. Plaintiffs Have Raised No Meaningful Dispute to the Prior Art Combination

Plaintiffs’ remaining laundry list of reasons the prior art is not identical to the asserted claims amounts to a challenge that CN’268 and Gibbs are not anticipatory, but that is irrelevant to an obviousness analysis. *Compare* 35 U.S.C. § 102 (anticipation) *with* § 103 (obviousness). Dr. Friedman, as Plaintiffs’ medical expert, provided no opinions about the Gibbs or CN’268 references whatsoever. Tr. 762:20-763:4. And Dr. deVries’s testimony is not credible at least because her testimony directly contradicts the express language of the prior art. For example, CN’268 states on its face that the addition of magnesium to doxycycline was used in part “to remarkably increase the solubility and pH value of doxycycline hydrochloride while enhancing the stability of the injection.” DTX-0014_0004. Nevertheless, Dr. deVries baldly denied at trial

that a POSA could understand CN'268 to say exactly that: that magnesium improved the solubility or stability of the CN'268 doxycycline formulations. Tr. 815:4-7. In other words, Dr. deVries's representations would have a POSA willfully ignore the express statements. Because Plaintiffs still dispute every single aspect of the claims, Nexus addresses each of them in this section:

a) *Plaintiffs' pH Arguments Are Irrelevant and Misguided*

Plaintiffs' various challenges regarding pH are irrelevant and do not affect the obviousness of the claims. *See* D.I. 249 at 38-39. For both reconstitution and diluted pH, a POSA would have known from CN'268 that adding magnesium would allow preparation at a higher pH than the old Minocin IV product. D.I. 250 at § IV.D.3. For the reconstituted vial pH, a POSA would know the prior art reported pH could be increased based on CN'268 or Gibbs. The case is even easier for the administered IV pH. In fact, Dr. deVries could not assume the hypothetical to formulate a response if Nexus's construction is applied. Tr. 890:8-892:15. The old Minocin IV product already provided a reasonable baseline of pH 4.5-6.0 for Lactated Ringer's and pH 2.5-4.0 for all other diluents. DTX-0112_0013; Tr. 480:10-17. So the Lactated Ringer's pH already covered the now-claimed ranges, and even for all the other diluents, there is overlap at pH 4.0 between the prior art and all claims except claim 7 of the '802 patent, which starts at pH 4.5. Knowing that the baseline examples included or were very close to the claimed pH range without magnesium, and knowing that magnesium increases pH, a POSA would have reasonably expected to achieve pH values within the claimed range. *See, e.g., In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990) ("more than 5%" claims obvious where prior art taught "about 1-5%"); *In re Brandt*, 886 F.3d 1171, 1177 (Fed. Cir. 2018) ("less than 6 pounds per cubic feet" claims obvious where prior art taught "difference between abutting ranges was "virtually negligible").

Dr. Friedman's unsupported allegation that Lactated Ringer's was not the "standard of care," D.I. 249 at 39, is entirely irrelevant to the obviousness analysis. Obviousness focuses on

comparing prior art publications with what is claimed. None of the asserted claims rule out Lactated Ringer's, so it is irrelevant here whether people actually used Lactated Ringer's or not. Dr. Friedman clearly admitted "it is known [from the prior art label] that you could use Lactated Ringer's to dilute the formulation" and the administration pH for that "standard option available to the person of ordinary skill in the art was 4.5 to 6.0." Tr. 727:14-19, 728:3-6. That is enough for obviousness. *See, e.g., Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1329 (2017) (obviousness does not require "the preferred, or most desirable" options) (internal citations and quotations omitted). Moreover, Dr. Friedman's allegation is not credible because he couldn't cite to any support for this allegation, Tr. 727:20-24, yet Plaintiffs deleted Ringer's but kept Lactated Ringer's on the label and did stability testing for it. DTX-0072_0008, 0011.

b) *Gibbs and CN'268 Taught How to Modify Minocycline Formulations*

Plaintiffs’ and Dr. deVries’s allegation that Gibbs does not disclose minocycline formulations is not credible at least because Gibbs expressly disclosed details regarding minocycline formulations and expressly identified “minocycline” as the drug for formulation dozens of times in only 4 pages. *See* Tr. 491:16-492:4. Gibbs used minocycline and doxycycline interchangeably. *Id.* Obviousness does not require only copying what the prior art did in a specific published example, because otherwise nothing could be obvious since obviousness is based on combinations of prior art teachings. *See KSR*, 550 U.S. at 421.

c) *Other Excipients Were Not Needed In The Prior Art*

Plaintiffs claim the prior art taught the “necessity” of other stabilizing or solubilizing agents for any minocycline formulation, but they ignore their own witness’s admissions. D.I. 249 at 39, 40. Dr. deVries admitted Gibbs reported the antioxidant was “optional,” *i.e.* not necessary to the formulation. Tr. 895:23-896:5. Dr. deVries also admitted CN’268 used a dissolvent explicitly for

the purpose of storage at a particular low temperature. Tr.895:3-7. The old Minocin IV product was only stored at room temperature, Tr. 481:11-19; DTX-0112_0013, so as such would not have required a dissolvent when applying the teachings of CN'268.

Similarly, as Dr. Klibanov explained, a POSA would have understood CN'268 to report that magnesium and not any other excipient increased solubility, stability, and tolerability of the tetracycline formulation. Tr. 488:19-25. So even though a POSA would consider the presence of other excipients in the formulations, a POSA would not expect others to be necessary. Tr. 488:5-18. As Dr. Klibanov explained, a POSA “would be cognizant that you only add excipients if they’re needed, and therefore if for an intravenous formulation of minocycline those [other stabilizing or solubilizing] excipients are not needed, which they are not, then they would not be added.” Tr. 491:6-10. Dr. deVries also agreed with this approach, confirming that the Broadhead IV formulation reference she introduced said to “keep it simple,” which she agreed meant “avoid excipients that you don’t need.” Tr. 856:1-14.

In addition, this argument does not apply to claim 27 of the '105 patent, because that patent does not exclude solubilizing agents or stabilizing agents.

d) *The Claimed Molar Ratios Were Obvious in View of the Prior Art*

Plaintiffs also incorrectly allege “Gibbs and CN'268 do not teach or suggest anything regarding the significance of using a high molar ratio of magnesium cations.” D.I. 249 at 40. There is no basis to such a claim: Dr. Klibanov explained at trial that CN'268 explicitly taught the benefits of magnesium would be achieved when used at “higher content,” meaning used in higher “molar ratios” than doxycycline. Tr. 486:1-6. Gibbs also explained that its formulation required metal complexes between minocycline and magnesium, and taught that molar ratios of up to 8:1 would be suitable for this purpose. Tr. 491:16-492:13. In addition, as an alternative basis for invalidity—and as explained in Nexus’s opening brief—a POSA would have been able to identify

an ideal molar ratio based on routine experimentation, and nothing in the prior art would have discouraged a POSA from doing so. *E.g.*, D.I. 250 at § IV.F.1.c.

Plaintiffs' allegation that "Dr. Chambers admitted that CN'268 teaches an excess of doxycycline to magnesium," D.I. 249 at 40, is misleading and irrelevant. Plaintiffs did not ask Dr. Chambers about the claimed molar ratios, and did not ask about whether CN'268 also teaches more magnesium than doxycycline. Based on the text of CN'268, Dr. Klibanov explained at trial that CN'268 explicitly taught to a formulator that magnesium was used in higher "molar ratios" than doxycycline. Tr. 486:1-6. Neither Dr. deVries nor Dr. Friedman rebutted this. Dr. Chambers provided opinions as a "POSA physician," not as a formulator, Tr. 615:23-616:9, just like Plaintiffs' medical doctor. Tr. 762:20-763:4. And to that end, Dr. Chambers addressed the medical aspects of CN'268, which went unrebutted. Tr. 622:20-625:5.

e) *A POSA Would Have Considered Both IM And IV Formulations*

Plaintiffs additionally argue that a POSA would not extrapolate from intramuscular to intravenous because intramuscular formulations *may* accommodate suspended solid particles (*i.e.* can be aqueous solutions or not) while intravenous formulations cannot (they are aqueous), but that is no reason to *ignore* all intramuscular formulations. D.I. 249 at 40. There is no dispute that CN'268 was in fact an aqueous solution. *See, e.g.*, Tr. 486:25-487:5 (Klibanov). Dr. deVries could not have provided credible testimony on this point, based on her nearly-nonexistent experience with injectable formulations, as opposed to oral formulations. Tr. 196:19-197:3; 851:18-852:6; 873:15-16. As Dr. Klibanov explained, both IM and IV are considered injectable formulations, and share relevant characteristics for formulation, which is what a POSA would consider as comparable formulations. Tr. 487:6-12. Dr. Klibanov also explained it is a formulator's job and routine practice to adjust excipients based on known characteristics, including route of administration. Tr. 465:8-24. Plaintiffs do not dispute the differences between intramuscular and

intravenous formulations were known, and a POSA would easily be able to apply the knowledge from one parenteral formulation to another using their knowledge and experience. *See KSR*, 550 U.S. at 421 (a POSA is “a person of ordinary creativity, not an automaton”). Dr. Chambers also explained that IM formulations are informative regarding tolerability of similar IV formulations and a POSA “would expect [reduced] toxicity at the site of injection [in an IM formulation] would translate to improved tolerability if given intravenously.” Tr. 623:12-23.

f) *Plaintiffs’ Admissions Render Any Disclosure Of RBC Hemolysis Irrelevant, And Improved Tolerance Was Taught*

Finally, Plaintiffs note the prior art does not mention hemolysis of red blood cells. D.I. 249 at 39. That is because it is not a standard recognized condition, as explained in Nexus’s opening brief. D.I. 250 at § V.B. Despite this, Nexus demonstrated at trial that a POSA would have reasonably expected reduced toxicity in view of the prior art. *Id.* at § IV.F.1.e. In fact, Dr. Chambers explained—and Plaintiffs never even attempted to rebut—that CN’268 specifically disclosed tissue toxicity which includes the same blood toxicity issues discussed in this case. Tr. 622:20-623:8. Therefore, even if Nexus had to show a reasonable expectation of success to achieve this property based on its disclosure in the prior art, Nexus did so. But as a separate and alternative basis, Nexus does not have to show any reasonable expectation of success or even disclosure in the prior art, because Plaintiffs have admitted that the reduced hemolysis limitation is an inherent property (D.I. 249 at 17), so this limitation does not need to be separately addressed. D.I. 250 at § IV.F.1.e.

B. Plaintiffs Provide No Evidence to Support Their Secondary Considerations

Because Plaintiffs’ experts gave up so much ground on prima facie obviousness, Plaintiffs’ briefing focuses on their rebuttal “objective evidence of non-obviousness,” commonly referred to as secondary considerations. But like the rest of their case, Plaintiffs only list conclusory

statements about each secondary consideration without plausible evidentiary support, and in most cases no documentary evidence at all. In doing so, Plaintiffs forget one critical thing: it is *Plaintiffs'* burden to produce evidence of any alleged secondary considerations. *E.g. Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1354 (Fed. Cir. 2013). They failed in multiple ways. Plaintiffs only distinguish old Minocin IV, when they were supposed to prove “comparison of the closest prior art.” *Pfizer*, 480 F.3d at 1370-71. Yet Plaintiffs regarded several references that already used magnesium such as the Isbister reference, DTX-0013, which Mr. Griffith knew about and yet Plaintiffs did not test. *See* Tr. 420:7-421:1-19. Plaintiffs also do not connect any secondary considerations to the osmolality requirement of the '105 patent. In short, Plaintiffs never overcame the strong evidence of obviousness and their experts' own admissions. *See Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

1. There is No Reference Teaching Away From the Claims

Plaintiffs point to five references as supposedly teaching away from the claims, but all of the references are old and outdated, published well before the Gibbs and CN'268 references that changed the state of the art and taught toward magnesium formulations with minocycline. D.I. 250 at § IV.G.5. Regardless, the references do not actually say what Plaintiffs allege, and even if they did still would not rise to the Federal Circuit's level of teaching away. Doing something different is not teaching away. “A reference does not teach away if it does not criticize, discredit, or otherwise discourage investigation into the invention claimed.” *Galderma Lab 'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (internal quotations omitted). Plaintiffs' references never say not to use magnesium at the claimed molar ratios for IV formulations with pH around 4.5-5.5 and at most offer *alternative* options, so they do not teach away from the claimed invention. *Syntex (U.S.A) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (“that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that

combination”); *Galderma*, 737 F.3d at 738 (Fed. Cir. 2013) (“A reference does not teach away, however, if it merely expresses a general preference for an alternative invention.”).

Plaintiffs’ references do not point away from the claimed conditions. As long as the claim covers any area obvious over the prior art, then the entire claims are obvious. *See, e.g., In re Cuzzo*, 793 F.3d 1268, 1281 (Fed. Cir. 2015) (applying “long-established rule” that whole claim is obvious if one embodiment within the claim is obvious). Here, nothing teaches away from at least the lower claimed pH ranges starting at pH 4.0 or 4.5, for all asserted claims. Plaintiffs erroneously conflate suggestions that minocycline-magnesium will precipitate *under certain conditions* with a belief that it would precipitate under *all conditions*. But as Dr. Klivanov explained, drugs may precipitate under certain conditions but not others. Tr. 920:12-18. No evidence suggests a precipitation issue at pH 4.0 or 4.5, especially for the very low concentrations of 0.1 to 1 mg/mL that are actually used with either old or current Minocin IV. Tr. 286:15-287:8.

Oddly, Plaintiffs still assert deVries 2006 as relevant, when they said the opposite to the Patent Office. Tr. 874:20-875:13; DTX-0004_2866. deVries could not have taught away from anything, since it was the basis for the Patent Office’s obviousness rejection in the first place. *Id.* Indeed, deVries 2006 did not teach away since it did not discuss, much less discourage, IV formulations with the claimed pHs and molar ratios. *See Galderma*, 737 F.3d at 738. In fact, it taught aqueous solutions of minocycline with metal cations *were* prepared within the claimed pH ranges, which all include at 4 or 4.5. *See, e.g., DTX-0010* at [0070] (reporting suspension does not occur until “final pH in the range of from about 5 to less than about 8”).

Plaintiffs next turn to Barringer, citing an experiment of a 2:1 molar ratio of magnesium to minocycline at a single high pH (6.5), and claiming this ratio “caused the minocycline to become insoluble and precipitate out of solution.” D.I. 249 at 30. Plaintiffs’ argument has no nexus to the

scope of what is claimed, since the claims all start at pH 4.0 or 4.5, while the only pH considered in Barringer was 6.5 (and at the wrong molar ratio). Tr. 919:13-16. Dr. deVries also admitted Barringer does not “mention or suggest in any way to use a higher molar ratio than 2 to 1” or “mention or suggest anything about the significance of molar ratio” so it could hardly have taught away from those options. deVries 784:7-12. In other words, the fact that Barringer chose one ratio does not mean teach away from others—teaching away must be explicit not implicit. *See, e.g., Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1327 (2017) (“reasons a skilled artisan would prefer one [option] over the other does not amount to a teaching away from the lesser preferred but still workable option”). In *UCB*, the court found prior art disclosing certain ratios of ingredients and not others did not “teach away” from the claimed ranges. *UCB, Inc. v. Actavis Labs. UT, Inc.*, 65 F. 4th 679, 692-693 (Fed. Cir. 2023).

Plaintiffs also surprisingly bring back Barringer’s statement about absorption issues with metal cations (D.I. 249 at 30), even though Dr. Klibanov so forcefully confirmed that statement was limited to gastrointestinal absorption of oral formulations, which is completely irrelevant to intravenous formulations. Tr. 914:4-916:4. The fact that Plaintiffs still rely on this statement despite its utter irrelevance shows the lack of any evidentiary support.

Third, Plaintiffs cite to Berthon for the same point that at some high pH, minocycline and magnesium will precipitate just like any other drug, but that allegation is still insufficient to teach away for all the reasons discussed above. D.I. 249 at 31. Plaintiffs never address what conditions a POSA would consider from Berthon, such as molar ratio, concentration, and pH. To the contrary, Berthon taught “a striking similarity” between magnesium-doxycycline and magnesium-minocycline binding structures, only further teaching towards the application of CN’268 and Gibbs to minocycline formulations. Tr. 884:7-17 (deVries), DTX-0183_0005.

Fourth, Plaintiffs cite to Allen that Dr. deVries in turn reported as providing the “the same message” as Barringer, meaning relating to oral formulations. D.I. 249 at 31; Tr. 790:12-19. Allen even expressly noted oral incompatibility is related to “gastrointestinal absorption.” PTX 157 at MELINTA017254. Allen thus is irrelevant for the same reasons as above.

Fifth, Plaintiffs point to Pawelczyk, but Dr. deVries admitted that reported aqueous solutions of minocycline at pH 4.2 and 5.2 were *strong*, retaining 90% of their original activity at 7 days at 25°C. PTX 133 at MELINTA017482; Tr. 898:11-20. Since Pawelczyk confirmed pH 5.2 would work, and the asserted claims all include pH 5.2, the claims are all the more obvious in view of Pawelczyk. Pawelczyk never suggests against combining magnesium with minocycline and instead reported magnesium was one of the metal cations that did not harm minocycline even though its stabilizing effect was not found to be as “distinct” as aluminum’s, which is still not “teaching away” by any legal standard. PTX 133 at MELINTA017490, 93. Moreover, the single study in Pawelczyk on magnesium was conducted at a single pH of 4.36 and a single (low) molar ratio of Mg²⁺-to-minocycline. *Id.* Even for that example, a POSA would have found Pawelczyk to show magnesium and minocycline *could indeed be prepared* at pH 4.36, which falls within the asserted patent claim ranges, so there was no teaching away from what the claims cover.

2. Plaintiffs Did Not Meet Their Burden On Unexpected Results

In their brief, Plaintiffs say their conclusory allegation about unexpected results was “unrebutted,” blatantly ignoring the extensive testimony by Drs. Klibanov and Chambers, as well as the numerous admissions by Plaintiffs’ own experts. Drs. Klibanov and Chambers showed that CN’268 and Gibbs expressly taught everything Plaintiffs now claim was somehow unexpected. Specifically, (1) Gibbs—and several other references discussed at trial—taught molar ratios of magnesium cations greater than 3:1 and up to 8:1; (2) CN’268 expressly taught adding magnesium would allow for increased pH, while the prior art Minocin IV product already used minocycline

formulations with pH at and above 4.0; (3) Plaintiffs raised no evidence of any doubt or problem with the pH 4.0 or pH 4.5 that all of the asserted claims include; and (4) both Plaintiffs themselves and Plaintiffs’ experts admitted that administration volumes below 500mL were already known and used in the prior art, and would have been expected by “normalizing pH.” D.I. 250 at § IV.F.3. Since Plaintiffs failed to show that anyone would expect failure using pH 4.0 or 4.5 with the claimed 3:1 or 4:1 molar ratios, or that these were somehow special, they failed to show any nexus between the prior art and the entire claim scope. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). “[U]nexpected results must be established by factual evidence,” which they are not here. *See In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). “Mere argument or conclusory statements” by patentee “do[] not suffice.” *Id.* Additionally, as explained in Nexus’s opening brief, Plaintiffs cannot show differences between the prior art and the claimed formulation, other than minor differences in degree and not kind, which are insufficient. D.I. 250 at § IV.G.4.

3. Plaintiffs Did Not Meet Their Burden on Long-felt Need

For the reasons explained in Nexus’s opening brief, Plaintiffs raised no evidence of long-felt but unmet need. D.I. 250 at § IV.G.2. Plaintiffs’ opening brief only highlights their deficiencies, further showing Plaintiffs cannot cite to any evidence criticizing the old Minocin IV product and thus cannot meet their burden to “point to an *articulated identified* problem and evidence of efforts to solve that problem, which were, before the invention, unsuccessful.” *Apple Inc. v. Samsung Elecs. Co.*, 816 F.3d 788, 804-05 (Fed. Cir. 2016), vacated in part on other grounds *reh’g en banc*, 839 F.3d 1034 (Fed. Cir. 2016) (internal quotations omitted). Plaintiffs claim Dr. Friedman’s testimony of his own clinical experience is “unrebutted,” but the testimony was rebutted because Dr. Chambers said there was no problem and Dr. Friedman’s anecdotal testimony was completely unsupported. *In re Kahn*, 441 F.3d 977, 990-91 (Fed. Cir. 2006) (law “requires that [patentee] submit actual evidence of a long-felt need, as opposed to argument”). Dr. Friedman

had no documentary support, Tr. 183:25-184:12, and couldn't even point any of his own documentation despite his prolific publication history: no adverse event reports, no patient reports, no articles. Tr. 752:5-753:20. In any event, any need was “short” felt, because Plaintiffs’ invention came immediately after CN’268 provided the solution in 2008. Pretrial Order Ex. 1 at 36.

Plaintiffs baldly assert Dr. Friedman cited to prior art “expressly teaching” the old formulation “was known to cause injection site tolerability issues,” but he did no such thing. Dr. Friedman and Plaintiffs cite broadly to two references supposedly related to this premise: Klein and Sweetana. *See* D.I. 249 at 33 (citing Pl. FOF ¶¶ 55, 180, 181). Klein does not reference the old Minocin IV formulation at all. PTX 182. Sweetana does nothing more than list the Minocin IV product with reconstituted pH and other formulation characteristics among dozens of drugs in a table. PTX 233 at MELINTA017409. At no point does either reference support Plaintiffs’ conjecture that there was any problem with the old Minocin IV product. In fact, the one reference that did have tolerability data regarding the old Minocin IV product—the Clark reference—reported no incidences of “injection site hemolysis,” only one incident of phlebitis that was not even attributed to the drug, and four incidences (less than 4%) of thrombophlebitis which were considered “minor.” PTX 164 at MELINTA017251; Tr. 437:9-438:24.

Plaintiffs also allege Mr. Griffith provided testimony on “known clinical problems” of the prior art formulation. D.I. 249 at 33. As a preliminary matter, Mr. Griffith is not a doctor nor does he even met the standard for a POSA, Tr. 381:10-382:3, so his testimony has little weight. *See Kyocera Senco Indus. Tools, Inc. v. ITC*, 22 F.4th 1369 (Fed. Cir. 2022). Regardless, Mr. Griffith’s testimony was only based on specific warnings and side effects listed on the old Minocin IV label, which he also admitted are *still* present in the current Minocin IV label. *See, e.g.*, Tr. 329:6-331:18. Plaintiffs cannot take credit for solving any need without evidence of change. *See, e.g., Geo M.*

Martin Co. v. Alliance Machine Sys. Intern. LLC, 618 F.3d 1294, 1304 (Fed. Cir. 2010).

Plaintiffs claim Dr. Chambers has no evidentiary support for his testimony that there were no problems with the pH of the old product and only administration pH under 2 would generally be of concern. D.I. 249 at 33. It is Plaintiffs' burden to prove problems were reported; not Nexus's burden to prove a negative. Regardless, Plaintiffs are wrong about the evidence. As Dr. deVries admitted, Broadhead said the same thing as Dr. Chambers: formulations administered at pH 2-12 generally "can be tolerated" "in practice." Tr. 853:16-23; PTX 225 at MELINTA017609.

Ultimately, Plaintiffs can do nothing more than point to the known pH of the old Minocin IV formulation and simply assume there were problems. That is not enough to show a long felt need. *See, e.g., Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332 (Fed. Cir. 2009) (mere drawbacks of the prior art do not establish long-felt unmet need); *In re Gershon*, 372 F.2d 535, 539 (C.C.P.A. 1967) ("The failure of the prior art to mention a problem may be due to the fact that in practice the problem is not a serious one or that a large number of satisfactory solutions is readily apparent."). Plaintiffs never achieved physiological pH (around pH 7.0), so there is no nexus between their assertion that neutral pH was important and the claimed invention. Plus, Plaintiffs haphazardly mix and match between what they say the claim covers (the pH of the reconstituted vial) and the potential product for any benefit (the administered IV bag).

Plaintiffs cite to three cases, D.I. 249 at 35, each of which support a finding of obviousness here. In *Depomed*, the court rejected alleged long-felt need because it had been presented only using "conclusory inventor testimony that there was a long-felt need" "without citing any evidentiary support." *In re Depomed, Inc.*, 680 F. App'x 947, 953 (Fed. Cir. 2017). The same is true here. In *Tris Pharma*, the court focused on the fact that there had been numerous commercial formulations of the drug at issue developed and "none of the many iterations" met the long-felt

need. *Tris Pharma, Inc. v. Actavis Lab'ys FL, Inc.*, No. 2021-1495, 2022 WL 2525318, at *5 (Fed. Cir. July 7, 2022). In contrast, here there was only one commercial Minocin IV product, and on top of that intervening prior art explaining exactly what to do to improve that product. Plaintiffs' blatantly overlook the new CN'268 (2008) and renewed demand for the old Minocin IV product (2009) on the eve of the 2010 patent priority date. Tr. 707:11-708:1 (Friedman). *Leo Pharm* is similarly distinguishable, because here months—not decades—passed between the key CN'268 prior art and the patent. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1359 (Fed. Cir. 2013).

Plaintiffs no longer assert intervening time alone as a separate secondary consideration, but still include a throwaway sentence that “the length of the intervening time between first publication of the old label (1973) or Gibbs (1989) and the invention date of the patents-in-suit (2010) is additional objective evidence of non-obviousness.” D.I. 249 at 38. The law is the opposite: “[a]bsent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness.” *Iron Grip Baseball Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004)) (emphasis added). Plaintiffs cite to *Leo Pharm*, which only discussed time *within* the “long-felt but unsolved need” consideration. 726 F.3d at 1359.

4. Plaintiffs Cannot Show Copying Supporting Non-Obviousness

As explained in Nexus's opening brief, this factor has little relevance in this case and Dr. deVries admitted there was no tie between the copying here and any technical merits, as opposed to mere regulatory reasons. D.I. 250 at § IV.G.6; *see also Adapt Pharma. Ops. Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1375 (Fed. Cir. 2022). Plaintiffs claim it is “unrebutted” that Nexus could have copied the old formulation, but they themselves failed to show this option. Dr. deVries did not consider the requirements for an ANDA, ignoring that Nexus could not have logistically run tests against the old Minocin product as would have been required by FDA (PTX 174 at 9-10) and only claimed said “those regulations aren't coming to mind right now.” Tr. 902:5-11. As

Nexus’s Dr. Tawde confirmed—rebutting Dr. deVries’s testimony—the old “RLD1” formulation “was not available for development.” Tawde 129:05-10. Dr. deVries also ignored the years of uncertainty created by her alternative process. *See* Tr. 901:13-902:4 (deVries).

IV. THE ASSERTED CLAIMS ARE INVALID UNDER 35 U.S.C. § 112

Plaintiffs failed to rebut the clear factual and legal bases that the asserted claims are invalid pursuant to 35 U.S.C. § 112. However, even if the Court were to accept Plaintiffs’ conclusory arguments, those arguments support a finding of invalidity under obviousness because Plaintiffs consistently admit that a POSA would know how to vary and experiment with pH, osmolality and volume—just as shown in Nexus’s obviousness section above.

A. Plaintiffs Can’t Define “Injection Site Hemolysis” or How to Measure it

Plaintiffs’ argument that a POSA would understand “injection site hemolysis” merely relies upon unsubstantiated subjective assertions by Dr. Friedman. *See* D.I. 249 at 7 (citing FOF ¶¶ 62-63). The claim itself and the specification are the primary sources for purposes of indefiniteness. *See IBSA Institut Biochimique, S.A. v. Teva Pharms. USA, Inc.*, 966 F.3d 1374, 1380-81 (Fed. Cir. 2020). It is undisputed that a POSA would understand the term “hemolysis,” but the specification provides no guidance for “injection site hemolysis.” *See* Tr. 588:22-589:7. And “injection site hemolysis” is not defined there nor in the medical field. Tr. 595:2-11, 596:17-20. Plaintiffs try to cover up the lack of definition with a discussion of possible “clinical signs and symptoms” that hemolysis supposedly creates “downstream,” like phlebitis. Tr. 114:22-115:2, 696:5-20. Again, Dr. Friedman had no evidence other than his say-so. Tr. 597:9-17. He did not even consistently identify where the “injection site” is, showing it on the skin surface on a demonstrative but testifying it could be where the needle enters the vein or where the catheter extends some distance beyond vein entry. Tr. 739:15-740:16. He also provided no way to separate out effects between hemolysis at the injection site and hemolysis anywhere else in the body. Tr. 742:1-19.

Plaintiffs and their expert incorrectly allege that Hoover 1990 used the same model as that shown in the patent. *See* PTX 177; D.I. 249 at 10. Not so, for the reasons addressed above in the non-infringement section. And Hoover 1990 never defined “injection site hemolysis” anyway.

Because as explained above and in Nexus’s Opening Brief “injection site hemolysis” is not defined, tested, or measured in the specification, the claim limitation lacks written description and enablement. *See* D.I. 250 at § V.B-C. The focus of these inquiries is about the specification itself: does it show that the inventors possessed the claimed invention, and taught others how to make and use it? None of Plaintiffs’ data shows any connection or closes the gap between “hemolysis” only and “*injection site* hemolysis”—however defined. Tr. 597:18-600:25.

B. Plaintiffs Fail To Refute That All Asserted Claims Are Invalid for Lack of Written Description and Enablement Of the pH Limitations

Plaintiffs misunderstand the facts and the law regarding the invalidity of the pH limitations for lack of written description and lack of enablement. Contrary to Plaintiffs’ assertion, Nexus did show inoperable embodiments with respect to pH from Example 30, which was confirmed by experts from both sides. PTX 1 at Table 30; Tr. 526:2-527:14 (Klibanov); 885:17-24, 886:22-25 (deVries). Plaintiffs respond that even though Example 30 did not explain how to figure out what concentrations or pH values to use, a POSA could figure them out. D.I. 249 at 43. If so, that amounts to an admission that a POSA would have applied CN’268 and Gibbs in the same way—by applying them and optimizing variables—showing the asserted claims are obvious.

The enablement issue is particularly problematic for Plaintiffs because of their experts’ view that the prior art showed high pH ranges would not work because they would be insoluble. Dr. deVries testified that “increasing the pH of the old formulation would have caused precipitation and instability of the formulation.” Tr. 844:22-845:3. She even testified broadly that “minocycline is poorly soluble in aqueous solutions near or above pH 4.” Tr. 795:15-17. Yet the claims still

stake out the entire pH range up to pH 6 for the '802 patent and pH 7 for the '105 patent, without showing anyone could achieve adequate solubility throughout that full range. The enablement “doctrine prevents both inadequate disclosure of an invention and overbroad claiming that might otherwise attempt to cover more than what was actually invented.” *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012). There is no need for a separate showing of undue experimentation where, as here, the trial testimony and “specification's teaching is itself evidence” of non-enablement. *AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234 (Fed. Cir. 2003).

The case law Plaintiffs rely on does not apply here. In *Alcon*, the patent challenger merely alleged that the claims were broader than the specification's disclosure. *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1188-91 (Fed. Cir. 2014). Here, however—as in *Biogen*—the claims expressly cover the result of intravenous administration across a broad array of pH, concentrations, and molar ratios. *See Biogen Int'l GmbH v. Mylan Pharma. Inc.*, 18 4th 1333, 1343 (Fed. Cir. 2021) (holding expressly claimed results require more support in the specification). Similarly, Plaintiffs' reliance on *Atlas Powder* is misplaced. One cannot “simply disavow the invalid portion and keep the valid portion of the claim.” *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1368 (2012). Nexus showed on cross-examination that there are inoperable embodiments of the asserted claims disclosed in the specification itself. In another case with a more similar factual scenario, the Federal Circuit held that enablement of five out of six permutations is not full scope enablement. *Trustees of Boston Univ. v. Everlight Elecs. Co.*, 869 F.3d 1357, 1363-65 (Fed. Cir. 2018). The asserted claims are not enabled to their full scope.

C. Plaintiffs' Arguments About the Volume Range In Claim 18 of the '802 Patent Confirm Invalidity

Claim 18 of the '802 patent recites, “The method of claim 1, wherein the total volume of the composition administered is less than 500 ml.” PTX 1 at Cl. 18. Plaintiffs argue that a POSA

would be able to determine an appropriate administration volume. While obviousness requires showing a POSA would be able to determine *any* operable volume less than 500 mL, full scope enablement means Plaintiffs had to show how to use *all* volumes that are claimed. For purposes of obviousness, Plaintiffs admit that “a POSA would know based on...background knowledge how to administer formulations at very small volumes; how to adjust volume, administration rate, and dosing frequency as needed to administer a therapeutically effective amount; and not to go so low as to affect efficacy or safety.” D.I. 249 at 44-45. For purposes of enablement, however, Plaintiffs cannot now rewrite the claims to say “less than 500 mL *but more than capable to safely administered.*” That is not what the claims say.

D. Plaintiffs’ Arguments About the Osmolality Range In Claim 27 of the ’105 Patent Confirm Invalidity

Similar to the administration volume claim, Plaintiffs try to rewrite their osmolality claim to only encompass some subset that a POSA could figure out. D.I. 249 at 44. But while that may help show obviousness, it does not justify the claims as written. Claim 27 of the ’105 patent is invalid for the same reasons described in Nexus’s Opening Brief. D.I. 250 at § V.F.

V. CONCLUSION

For the above reasons, Plaintiffs failed to meet their burden to prove direct or indirect infringement, did not rebut Nexus’s clear and convincing obviousness showing, did not prove adequate or relevant secondary considerations, and failed to rebut invalidity under Section 112. The Court should, therefore, find Nexus is not liable for infringement, the patents are invalid as obvious, and the patents are invalid under Section 112.

Dated: July 26, 2023

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CERTIFICATE OF SERVICE

The undersigned certifies that on July 26, 2023, the foregoing document was served on counsel of record by operation of the Court's CM/ECF system.

/s/ Matthew Wilkerson

**IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS**

MELINTA THERAPEUTICS, LLC,
MELINTA SUBSIDIARY CORP., and
REMPEX PHARMACEUTICALS, INC.,

Plaintiffs,

V.

NEXUS PHARMACEUTICALS, INC.,

Defendant.

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)
)
) C.A. No. 1:21-cv-02636
)
)
) Judge John F. Kness
) Magistrate Judge Maria Valdez
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NEXUS PHARMACEUTICALS, INC.’S
PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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PROPOSED FINDINGS OF FACT

I. BACKGROUND

1. Nexus filed an Abbreviated New Drug Application (“ANDA”) to develop a generic version of the only minocycline IV product on the market at the time it filed. The ANDA included a certification that the patents-at-issue are not infringed and invalid. After Nexus’s ANDA filing and associated patent certification, Plaintiffs filed this litigation.

2. Minocycline is an old drug that was used since the 1970s, nearly 40 years before the May 2010 priority date of the asserted patents. *See* PTX 155; Tr. 75:17-19 (Friedman). Minocycline is a second-generation antibiotic in the tetracycline class, and minocycline and doxycycline are the second-generation tetracyclines. Tr. 472:21-474:1 (Klibanov); Tr. 606:12-16 (Chambers).

A. The Asserted Claims

3. Plaintiffs assert claim 27 from U.S. Patent No. 9,278,105 (“the ’105 patent”) and claims 1, 7, and 18 from U.S. Patent No. 9,084,802 (“the ’802 patent”) (collectively, “the asserted claims”). *See, e.g.*, D.I. 226.

4. All of the asserted claims are method claims that require the administration of minocycline IV containing magnesium to achieve certain claimed features. PTX 1 at Cl. 1, 7, & 18; PTX 2 at Cl. 27.

5. Asserted claims 1, 7, and 18 of the '802 patent are provided in full below. Claims 7 and 18 depend from claim 1, meaning that they each additionally include all requirements of claim 1.

1. A method of treating a bacterial infection in a subject, wherein the method consists of:
administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration.

wherein the molar ratio of magnesium cation to minocycline is greater than 4:1,
and

wherein the composition has a pH that is no less than 4 and no greater than 6,

7. The method of claim 1, wherein the composition has a pH between about 4.5 to

18. The method of claim 1, wherein the total volume of the composition

6. Asserted claim 27 of the '105 patent depends from claim 1, meaning that it includes

1. A method of treating a bacterial infection in a subject, wherein the method

27. The method of claim 1, wherein the 7-dimethylamino-tetracycline is

7. Each of the asserted claims of the '802 patent require “reduced injection site

8. Claim 27 of the '105 patent depends from claim 1 and requires an “osmolality less

B. The Minocin IV Products

9. Minocin IV was commercially available since the 1970s. DTX-0072 0004. The

11. Shortly after acquiring the NDA for the old Minocin IV product, Plaintiff Rempex applied for approval to modify the old formulation to the current version, using a supplemental NDA or “sNDA.”

13. Plaintiff Rempex explained to the FDA that the current minocycline formulation is to be used “for the same indications using the same dosage regimens” as the old formulation, with “no change in infusion time.” *Id.* at 0007.

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15. The current minocycline formulation's label and the prior art minocycline formulation's label contain the same indications. Tr. 582:7-10 (Chambers). The two minocycline formulations' labels also include substantially the same warnings for adverse events, with the current minocycline formulation only adding adverse events related to the addition of magnesium. *Id.* at 581:14-18, 582:11-12. Both say "If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result." DTX-0110, DTX-0112 at "Dosage and Administration". Both report "injection site erythema" and "injection site pain" as "Local Reactions." *Id.* at "Adverse Reactions". Both report "hemolytic anemia" as a blood reaction. *Id.*

C. The Parties' Expert Witnesses

1. Nexus's expert witnesses

16. Nexus called Dr. Alexander Klibanov, Ph.D. as an expert in medicinal chemistry and pharmaceutical formulation. Dr. Klibanov has more than 40 years of experience as an organic chemistry researcher and professor at M.I.T, and with over 300 publications in his field and the publications were recognized as within the top .01% of research according to a Stanford University survey. Tr. 459:18-460:18 (Klibanov). Dr. Klibanov has obtained several issued patents and has served as a consultant for pharmaceutical, chemical, and biotechnology companies where his work has included work on antibiotic formulations for tetracyclines and minocycline, among others. *Id.* at 460:19-461:7. He has been qualified as an expert in pharmaceutical formulation in patent cases for both plaintiffs and defendants. *Id.* at 461:23-462:11. Unlike Dr. deVries, Dr. Klibanov has extensive experience regarding the formulation of intravenous pharmaceutical formulations. *Id.* at 464:6-15.

17. Nexus called Dr. Henry Chambers, M.D. as an expert in the field of treatment of infectious diseases and the use of antimicrobial agents, including tetracyclines and minocycline. Dr. Chambers has 40 years of experience as a clinician, researcher, and professor focusing his

18. Plaintiffs called Dr. Bruce Friedman, M.D. to testify as an expert in treating infectious diseases in critically ill patients using minocycline. While Dr. Friedman used minocycline with patients, his practice was limited to certain treatments and he did not testify as to any experience that he had with the use of tetracyclines in the field more generally. Tr. 72:18-73:5 (Friedman). Dr. Friedman has never published an article regarding any improvement of Plaintiffs' minocycline product over the prior art formulation. *Id.* at 753:9-20.

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II. AFTER INITIALLY AGREEING NO CLAIM CONSTRUCTION WAS NECESSARY, PLAINTIFFS BELATEDLY RAISED CLAIM CONSTRUCTION ISSUES AT TRIAL

20. This Court entered a Scheduling Order that provided a schedule for exchanging and briefing claim construction issues before the close of fact discovery and commencement of expert discovery. D.I. 36.

21. In February 2022, even after having seen Nexus's contentions, Plaintiffs still informed Nexus that no claim terms required construction. D.I. 248, Ex. A. In reliance on that representation, the parties jointly informed the Court that claim construction was unnecessary. D.I. 70.

22. But at trial, Plaintiffs belatedly included testimony from their experts on new claim constructions for five terms—"administering," "composition," "consists of/consisting of," "subject," and "does not include magnesium."

A. "Administering" (all asserted claims)

23. Each of the asserted claims require "administering" a minocycline formulation. PTX 1, Cl. 1; PTX 2, Cl. 1.

24. The specifications for the patents-in-suit do not provide a specialized definition of "administration," nor require dilution as part of administration.

25. Example 13 itemizes fourteen different formulations, the first eight of which are "for intravenous administration" without mentioning dilution. PTX 1 at 38:1-39:55.

26. The patent specifications refer to administering an "admixture" to "patients," but neither of those terms are in the claims. PTX 1 at 13:47-56.

B. “Composition” (all asserted claims)

27. The asserted claims state that the “method of treating a bacterial infection” is achieved by “administering a therapeutically effective amount of a composition.” *See, e.g.*, PTX 1, Cl. 1; PTX 2, Cl. 1.

28. “Composition” refers to what is administered and can take many forms, so the claim language itself informs what is administered. The specification is the same for both asserted patents, and the shared specification describes the invention including “methods of treating or preventing a bacterial infection in a subject comprising administering the pharmaceutical composition... to the subject via an intravenous route of administration.” PTX 1 at 6:26-30, 6:31-36.

29. The specification further refers to administering “less than 200 mL of the composition” and “administering the composition in less than 60 minutes.” *Id.* at 6:37-41. The specification and other claims provide different administration volumes (including “less than 50 mL”) and times (including “less than 10 minutes”). *Id.* at 19:39-58; 42:3-8.

30. The pH limitations of the claims are clinically meaningful only for what is actually administered. Tr. 480:18-22 (Klibanov); 721:10-13 (Friedman).

31. The osmolality limitation of the ’105 patent is clinically meaningful only for what is actually administered because it relates to patient tolerance. Tr. 136:15-137:2 (Friedman).

32. Reduced injection site tolerability, or any alleged reduction in injection site hemolysis, cannot occur unless the composition is administered. Tr. 738:13-739:3 (Friedman); 893:14-16 (deVries).

33. The shared specification does not limit the claimed “composition” to the ephemeral intermediate reconstituted product. The specification states: “some *compositions* include solutions

resulting from diluting those reconstituted solutions with pharmaceutically acceptable diluents for use intravenous bags.” PTX 1 at 12:31-34 (emphasis added).

C. “Consists of” And “Consisting of” (Claims 1, 7, 18 of the ’802 patent)

34. The '802 patent uses “consists of” three times in a row. *See* PTX 1, Cl. 1.

35. The asserted claims do not recite “diluent” nor do they narrowly describe the precise method of administration conducted in the clinical setting.

D. “Subject” (all claims)

36. The asserted claims each refer the term “subject” rather than the word “human.”
PTX 1, Cl. 1; PTX 2, Cl. 1.

37. Administration to humans is an embodiment of the broader claimed administration to a “subject.”

38. The patents use the term “subject” throughout the specification, and uses “human” only in Example 12, and otherwise tests different animal models. *See, e.g.*, PTX 1 at 29:56-32:30, 37:7-67, FIG. 1-5.

E. “Does Not Include Magnesium” (claims 1, 7, 18 of the ‘802 patent)

39. The term “does not include magnesium” is a limitation of the asserted claims of the ‘802 patent.

40. The asserted claims include two references to magnesium alone and no other metal. The claims refer to the claimed formulation that has “a magnesium cation” and then the comparator formulation that “does not include magnesium.” PTX 1, Cl. 1.

41. The specification explains that metal cations include “common” examples like “iron, copper, zinc, manganese, nickel, cobalt, aluminum, calcium, magnesium and gallium.” *Id.* at 10:4-9.

III. PLAINTIFFS FAILED TO MEET THEIR BURDEN TO SHOW INFRINGEMENT

42. Plaintiffs allege Nexus is liable for indirect infringement, and do not assert any allegations that Nexus is a direct infringer of the asserted claims. D.I. 228, Pretrial Order, Section XV.A.

A. Plaintiffs Did Not Introduce Data Showing Direct Infringement Of The Osmolality Limitation of the '105 Patent

43. Plaintiffs failed to introduce any evidence of the osmolality of Nexus's product, whether in the intermediate reconstituted state or diluted for administration state. Plaintiffs did offer internal Melinta internal experimental research data for osmolality values, as supposedly applicable to Nexus's product. Tr. 262:7-263:8 (deVries). Plaintiffs failed to use any data, even their own data, corresponding to the correct reconstituted water volume conditions used in Nexus's ANDA product according to Nexus's label.

44. Under Plaintiffs' construction that the osmolality refers to the measurement of the drug reconstituted in the vial, Plaintiffs showed no minocycline formulation will infringe the osmolality limitation. Dr. deVries admitted she relied upon test data with the incorrect reconstitution volume. *Compare* Tr. 237:17-20 (testifying initially that the data relied upon is reconstituted in 5 mL of water) *with* Tr. 268:8-12 (testifying that the data she relied upon was in fact reconstituted in 10 mL of water, not 5 mL).

1. Under Plaintiffs' vial-focused construction of "administering a composition," there is no direct or indirect infringement

45. The labels for the old Minocin product, current Minocin product, and Nexus's ANDA product all instruct reconstituting with 5 mL of water. DTX-0112, DTX-0110, PTX 42.

46. Plaintiffs' expert testified that an osmolality test is "very easy" and takes "minutes." Tr. 254:15-24 (deVries). Plaintiffs' expert, Dr. deVries, did not conduct any tests on any minocycline product to support her opinions. Tr. 255:5-7 (deVries).

47. Plaintiffs' expert, Dr. deVries, relied only on Plaintiffs' own development records, prior to the production of any commercial product. Tr. 262:2-9 (deVries).

48. On direct examination and in response to the Court's query, Dr. deVries asserted that the data she showed related to vials with 5 mL of water added. Tr. 236:21-237:22, 239:13-25 (deVries). On cross examination, Dr. deVries admitted that the testing data she relied upon actually used 10 mL of water, which was expressly stated in the document. Tr. 268:8-12 (deVries).

49. Dr. deVries also testified that "a first guess approximately would be that the osmolality would double" when comparing a solution with 5 mL of water compared to the reported 10 mL of water. Tr. 307:20-308:4 (deVries).

50. Applying Plaintiffs' own expert's doubling approximation: the data relied upon by Plaintiffs using 10 mL of water for reconstitution ranged from 286-302 mOsmol/kg. Doubling those numbers results in a range from 572-604 mOsmol/kg. *See* PTX 197 cited in PDX-2039.

51. Thus, Dr. deVries's own data and testimony showed that each and every vial tested (and relied upon) by Plaintiffs would be well *over* the required 500 mOsmol/kg threshold required by claim 27 of the '105 patent. PTX 2 at Cl. 1.

52. Plaintiffs also failed to introduce evidence that Nexus knows the osmolality of the solution in a reconstituted vial. Plaintiffs failed to show that Nexus knew there would be patent infringement. The only evidence Plaintiffs offered at trial was Nexus's deposition testimony by Dr. Suprita Tawde who testified that the diluted formulation should be "isotonic." Tawde Dep. Tr. 73:23-74:9. However, Dr. Tawde's testimony made clear that she was only describing the diluted

formulation, not the reconstituted, and she did not know any numeric value for either because a particular osmolality “is not a requirement.” *Id.*

60. The standard of care does not specifically require 500 mOsmol/kg, but it's an approximation with some standard diluents having a greater osmolality, but still considered part of the standard of care. Tr. 681:9-22 (Chambers).

62. An approved diluent on the Minocin IV label, 5% dextrose and normal saline, has an osmolality greater than 500 mOsmol/kg, even before adding any drug particles that would make that number higher. Tr. 654:21-25, 681:9-22 (Chambers). Plaintiffs never disputed this testimony.

63. Claim 1 of the '802 patent requires a reduction of injection site hemolysis when administering the claimed formulation compared to administering a formulation without magnesium. PTX 1, Cl. 1. Claims 7 and 18 depend from claim 1, and also have the reduced injection site hemolysis requirement. PTX 1, Cl. 7, 18. All of these claims use the “consists of” language that the parties proposed for construction.

64. The '802 patent specification relies on *in vitro* hemolysis tests of rabbit red blood cells in saline solution. PTX 1 at 29:56-32:30.

65. The rabbit red blood cell test used by the '802 patent are known to be “sensitive to breaking down in hemolysis” and “the test conditions are overly sensitive and highly artificial.” Tr. 598:11-23 (Chambers). Because they are “sensitive” they represent a “worst-case test.” Tr. 836:13-837:13 (deVries).

66. The *in vivo* test that Plaintiffs conducted using actual IV administration was to evaluate venous tolerance in rabbit ear veins, and those three tests showed no difference between formulations with and without magnesium—even when very high drug doses were used. Tr. 864:17-870:23 (deVries); DTX-0041.

67. Plaintiffs' expert, Dr. deVries gave her understanding of the claim that the “same” formulation should be tested with and without magnesium to show infringement. Tr. 223:11-225:3 (deVries). Dr. deVries confirmed that opinion during cross examination. Tr. 292:9-293:12 (deVries).

68. Dr. deVries agreed that magnesium molar ratio, drug concentration, and pH all affected injection site hemolysis. Tr. 281:4-13 (deVries). Dr. deVries also admitted that formulations were compared against one another to establish a difference in injection site hemolysis that differed from one another for these three variables. Tr. 284:12-285:5 (deVries). The same formulation with and without magnesium was not tested for any hemolysis data reported.

69. For example, the test described by Figure 1 of the '802 patent compared “Mino-saline” formulations at pH 4.17 to “Mino-Mg” formulations at the significantly different pH of 5.85 using a 10:1 ratio of magnesium to minocycline. PTX001 at FIG. 1, 30:19-45. Thus, both the pH and the molar ratio were different from Nexus's product.

70. Mr. Griffith submitted a declaration to the Patent Office, in which he described a mouse subcutaneous injection test, where one mouse was injected with 10 mg/mL of minocycline at a pH of 2.60, and compared to another mouse injected with 10 mg/mL of minocycline and magnesium but with a pH of 5.43. PTX 196 at MELINTA003926. Thus, the pH of the formulations was different to each other, and the concentration was different from Nexus's product.

71. Plaintiffs' expert Dr. Friedman proposed a cascade theory based on his personal observations, which were not corroborated by documents or publications. Tr. 753:4-20 (Friedman). Nexus's expert Dr. Chambers pointed out that Dr. Friedman's cascade theory did not have support. Tr. 597:9-17, 632:20-23 (Chambers).

72. The U.S. Food and Drug Administration previously rejected Plaintiffs' allegations of improved tolerability. Plaintiffs previously asked FDA to allow them to claim improved tolerability on the product label for their formulations. DTX-0072_0006. FDA declined, stating that any actual "claims of superiority of your proposed formulation" containing magnesium would need to be justified by comparing in patients the old and proposed minocycline formulations, with "two superiority trials...designed to show better tolerance, less phlebitis" and the like. PTX 88 at 4. But rather than do the tests, Plaintiffs "acquired" the existing NDA, so they would not have to compete with the old Minocin formulation on the market, and "the clinical trial...to support label claims for improved tolerability was considered no longer necessary and was not conducted." DTX-0072_0006. Plaintiffs never conducted any comparative clinical study to show improved tolerability for the magnesium containing product as compared to a product without magnesium.

73. Dr. Friedman admitted that if Plaintiffs wanted to claim superiority in their label then they would have had to do a clinical study with the FDA. Tr. 165:8-16 (Friedman). Dr. deVries admitted that "If you want to make a claim about a clinical difference, you have to do a

clinical study. Tr. 250:24-251:10 (deVries). Yet, Plaintiffs did not conduct any clinical trial to show improvement. Tr. 170:4-18 (Friedman).

74. There is no evidence that Nexus has knowledge of whether its minocycline formulation results in “reduced injection site hemolysis.” Plaintiffs point to submissions referring to the magnesium sulfate’s role as a “hemolysis reducer,” which was based on a literature search and not any testing.

75. As to Nexus’s knowledge regarding injection site hemolysis, Dr. Tawde specifically testified that “Nexus did not do any studies to confirm the role. So whether it is true or not, Nexus does not know. Nexus just used the literature search—literature information.” Tawde Dep. Tr. 104:7-15.

76. Nexus and its label are indifferent to whether its product results in a reduction in injection site hemolysis. The old Minocin label, the current Minocin label, and Nexus’s label all have the very same warnings when it comes to injection tolerability issues. *See* DTX-0112, DTX-0110, DTX-0101.

77. Dr. Chambers explained that the warnings related to local reactions, blood, and thrombophlebitis are the same across the different formulations, so one cannot assert or claim one formulation having a benefit over the other. Tr. 592:24-595:10 (Chambers). This fact was not rebutted by Plaintiffs’ expert, Dr. Friedman. Tr. 182:1-9 (Friedman).

78. Plaintiffs’ expert, Dr. Friedman, agreed that a physician would look to the adverse events section of the label for adverse events such as injection site tolerability issues. Tr. 174:12-15 (Friedman).

90. FDA agreed the increased pH and lower volume did not justify a claim to improved tolerability. Dr. deVries explained, “if you want to make a claim about a clinical difference, you have to do a clinical trial.” Tr. 250:24-251:10 (deVries).

91. It is undisputed that higher pH options (diluting the formulation with Lactated Ringer’s for a pH of 4.5-6.0) and lower volumes (as Plaintiffs told FDA) with the old Minocin formulation. Tr. 728:3-6, 754:24-755:7 (Friedman).

92. Nexus’s corporate witness, Dr. Tawde, explained that “Nexus did not perform any studies to confirm the function of magnesium.” Tawde Dep. Tr. at 87:10-92:12. Rather, the FDA submission was only “based upon the literature.” *Id.* Nexus never tested for hemolysis, injection site hemolysis, or compared two formulations to one another for any hemolysis incidence. *Id.* at 97:20-98:3.

93. There is no evidence that FDA made any findings regarding magnesium’s function in Nexus’s product. FDA merely sought to confirm that Nexus’s formulation components were the same as Plaintiffs’ formulation, consistent with FDA regulations. Tr. 205:21-206:18 (deVries).

94. FDA never accepted magnesium as a hemolysis reducer, because it required more proof from Plaintiffs to make such a claim on its label, and Plaintiffs referred to magnesium as a “solubilizer/stabilizer” in its FDA filings. DTX-0131_0006; DTX-0057; Tr. 395:21-24 (Griffith).

95. Plaintiffs’ expert, Dr. deVries, admitted that claim 7 of the ’802 patent requires pH 4.5-5.5 and that the current minocycline formulation label for the administered composition allows pH 6.0, which does not infringe. Tr. 272:24-273:23 (deVries).

96. Claim 18 of the ’802 patent requires an administered volume less than 500 mL. PTX 1 at Cl. 18. Dr. deVries admitted that volumes above 500 mL are included on the Nexus label and do not infringe. Tr. 273:24-274:10, 274:24-275:7 (deVries).

97. Plaintiffs' experts testified that the adverse events from the old Minocin IV formulation label had to "stay[] in the label." Tr. 178:24-179:15 (Friedman); 251:11-19, 253:20-254:1 (deVries). Thus, both the current Minocin IV formulation label and Nexus's label contain the same warnings as the old Minocin IV label, and only *add* warnings directed to magnesium. Tr. 582:11-12 (Chambers).

IV. THE ASSERTED CLAIMS ARE OBVIOUS IN VIEW OF THE PRIOR ART

A. Person of Ordinary Skill in the Art

98. A Person of Ordinary Skill in the Art (POSA) for purposes of the asserted patent claims should be defined as:

A POSA in the subject matter of the patents-in-suit would have been an individual with an advanced degree in pharmacy, chemistry, chemical engineering, or a related field, plus practical experience with pharmaceutical formulations, including their methods of preparation, stability, characterization, and administration, along with a physician or medical professional who administers injectable formulations. For example, (s)he would have had a Ph.D. degree in those areas with about 1-3 years of practical experience or a master's degree with about 5-6 years of such experience.

99. The parties agree that a POSA should have experience formulating and/or administering pharmaceutical formulations, but Plaintiffs propose adding an extra requirement that the POSA would have experience with "tetracyclines" generally. *See, e.g.*, Tr. 463:23-464:2 (Klibanov); Tr. 204:4-7 (deVries).

100. As Dr. Klibanov explained at trial, a "tetracycline-only" formulator is not to be expected, as a formulator would be more likely to specialize in types of formulations such as aqueous injectable or oral solid formulations rather than experts a particular compound class. Tr. 474:18-25 (Klibanov).

102. Pharmaceutical formulations typically consist of an active drug substance and excipients. Tr. 465:1-7 (Klibanov).

104. In evaluating what excipients to add, a formulator would look to the prior art for the drug substance and similar drugs, and rely on their own common knowledge and experience. Tr. 465:12-16 (Klibanov).

106. Intravenous administration is a type of parenteral administration where the drug is injected through the skin and into the vein of a patient. Tr. 465:25-466:7 (Klibanov).

108. Both intravenous and intramuscular formulations are injected through a needle into the body. Intravenous formulations do not contain solid drug product and include a drug dissolved

116. It is generally desirable to have the osmolality of an intravenous formulation to be near the osmolality of blood, around 300 mOsmol/kg. Tr. 470:4-8 (Klibanov); 854:3-12 (deVries); PTX 225 at MELINTA017618.

C. Scope and Content of the Prior Art

119. Experts for both parties agreed that prior to the asserted patents, the drug minocycline had already long been used intravenously to treat bacterial infections. *E.g.*, Tr. 841:5-8 (deVries); Tr. 719:18-21 (Friedman); Tr. 475:19-24 (Klibanov).

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1. The Old Minocin IV product

121. An uncontested fact is that Minocin Prescribing Information, NDA 50-444/S-0457, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050444s045,050445s027lbl.pdf (“2007 Minocin IV Label” or “old Minocin IV label”) was published in January 2007 according to the FDA website, and is prior art to the asserted patents. Pretrial Order Ex. 1 (Uncontested Facts) at ¶ 40.

122. DTX-0112 is a true and accurate copy of the 2007 Minocin IV label. Tr. 477:6-10 (Klibanov).

123. The 2007 Minocin IV label describes the version of Minocin IV (“old Minocin IV product”) that was commercially available in the US before the May 12, 2010 priority date and associated information. Tr. 476:13-19 (Klibanov).

124. The 2007 Minocin IV label taught minocycline had been FDA approved for intravenous administration to treat various bacterial infections. DTX-0112; Tr. 477:25-478:5 (Klibanov).

125. The old Minocin IV product consisted of lyophilized (which means freeze-dried solid product) minocycline to be reconstituted in Sterile Water and “immediately” further diluted in one of various diluents prior to intravenous administration. DTX-0112_0001, 0013; Tr. 478:10-18 (Klibanov).

126. The old Minocin IV formulation contained 100mg of minocycline. DTX-0112_0013; Tr. 478:10-18 (Klibanov).

127. The old Minocin IV formulation reconstitution volume was 5mL. DTX-0112_0013; Tr. 478:10-18 (Klibanov).

128. The old Minocin IV label taught administration of the final diluted formulation was in a total volume of between 500 and 1000mL for adults. DTX-0112_0013; Tr. 478:10-18 (Klibanov).

129. The old Minocin IV label taught a weight-based dosage for pediatric patients, which included volumes less than 500 mL. DTX-0112_0013; Tr. 626:17-22, 627:2-8 (Chambers).

130. The old Minocin IV label taught use of the following diluents: Sodium Chloride Injection USP, Dextrose Injection USP, Dextrose and Sodium Chloride Injection USP, Ringer's Injection USP, or Lactated Ringer's Injection USP. DTX-0112_0013; Tr. 479:4-18 (Klibanov).

131. When diluted in Lactated Ringer's, the old Minocin IV label taught minocycline could be formulated and administered in aqueous solutions of pH 4.5-6.0. DTX-0112_0013; Tr. 480:10-17 (Klibanov); Tr. 727:14-19, 728:3-6 (Friedman).

132. When diluted in other diluents such as saline or dextrose the old Minocin IV label taught the final pH would be 2.5-4.0. DTX-0112_0013; Tr. 480:10-17 (Klibanov).

133. When diluted according to the old Minocin IV label, the formulation was stable for at least 24 hours at room temperature. DTX-0112_0013; Tr. 481:11-19 (Klibanov).

134. The old Minocin IV label taught the product had a pH ranging from 2.0 to 2.8 when in the intermediate reconstituted stage. DTX-0112_0001.

135. The old Minocin IV label taught reconstituting and diluting a formulation to be administered. DTX-0112_0013; Tr. 478:10-18 (Klibanov).

136. Both Dr. deVries and Dr. Klibanov testified that they expected the osmolality of the old Minocin IV product was less than 500 mOsmol/kg, either as a reconstituted or a diluted product. Tr. 308:6-9 (deVries); Tr. 512:14-24 (Klibanov). It was standard for intravenous

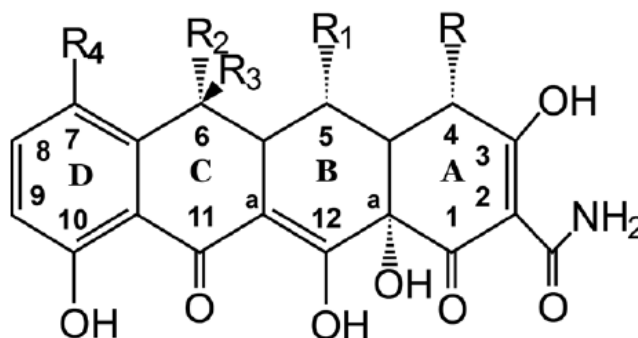
formulations to have osmolality near or about the osmolality of blood, which is about 300 mOsmol/kg. Tr. 762:16-19 (deVries); Tr. 470:4-8 (Klibanov).

137. Dr. Friedman admitted “it is known [from the prior art label] that you could use Lactated Ringer’s to dilute the formulation” and the administration pH for that “standard option available to the person of ordinary skill in the art was 4.5 to 6.0.” Tr. 727:14-19, 728:3-6 (Friedman).

2. Minocycline was known to have similar chemical structure and characteristics as other tetracyclines, including doxycycline

138. The minocycline compound is a member of a class of antibacterial drug compounds known as tetracyclines. Tr. 470:15-19 (Klibanov).

139. As of the priority date, tetracyclines were well known to have the following shared chemical structure:



Shared chemical structure of tetracyclines

Tr. 470:15-472:19 (Klibanov, citing DDX-2010). This common tetracycline structure comprises four fused rings (labeled above as A-D) made up of 12 carbon atoms (locations identified above by numbers 1-12) and contains various substituents attached to this common core structure. *Id.* While the various tetracycline compounds may have slight differences at the locations depicted

above by the letter R, they share the remaining substituents, including those at the bottom of the molecule (locations identified above by numbers 10, 11, 12, 1). *Id.*

140. As of the priority date, doxycycline and minocycline were the two second-generation tetracyclines, and were known to differ only at substituents in the top left portion of the molecules: at locations C-5, C-6, and C-7. *See* DTX-0174_0002, Fig. 1; Tr. 474:2-7 (Klibanov, discussing DDX 2011). The remainder of doxycycline and minocycline were known to be identical. *Id.* Similarly, minocycline differed from the tetracycline compound only at C-6 and C-7. *Id.*

141. While minocycline, doxycycline, and tetracycline were not identical compounds and thus did not have identical pharmaceutical applications, their characteristics were nonetheless very similar and they were identical for formulation purposes including along the bottom half, and a POSA would have readily looked to doxycycline and other tetracycline formulations from the prior art in searching for teachings on how to formulate minocycline. Tr. 475:1-14 (Klibanov).

3. Minocycline was known to complex with magnesium similarly to other tetracyclines

142. The prior art taught that magnesium was known to form complexes, or chelates, when combined with minocycline or other tetracyclines. *See, e.g.*, DTX-0174; PTX 152; DTX-0183; DTX-0012.

143. Plaintiffs' expert Dr. deVries admitted magnesium was known to complex with minocycline prior to the asserted patents. Tr. 843:17-19 (deVries).

144. The prior art reference Nelson 1998 explained magnesium complexation of tetracyclines had been studied extensively before the priority date, and that magnesium was known to bind with tetracyclines at the C-11 and C-12 locations, both on the lower half of a tetracycline compound including minocycline and doxycycline. DTX-0174_0004.

145. Dr. deVries admitted Nelson 1998 taught that tetracyclines bind to metals in the lower peripheral region. Tr. 899:15-19, 900:4-10 (deVries).

146. The prior art reference Barringer explained “[m]inocycline, *like the other tetracycline antibiotics*, forms strong chelates and salts with metal cations, and these metal cations include magnesium.” PTX 152_0011.

147. Prior art reference Berthon studied binding of magnesium to various tetracyclines, and concluded there is a “striking similarity” between the magnesium-doxycycline and magnesium-minocycline binding systems. DTX-0183_0005; Tr. 884:7-17 (deVries).

148. The prior art reference Gibbs taught formulations in which magnesium was added to either minocycline or doxycycline to form complexes, and a POSA would have understood this disclosure to teach that magnesium functions interchangeably with minocycline and doxycycline from a formulation standpoint. Tr. 491:16-492:4 (Klibanov).

149. A POSA would have known and expected doxycycline and minocycline to interact similarly with magnesium ions, and would have readily looked to doxycycline and other tetracycline formulations from the prior art in searching for teachings on how to formulate minocycline. Tr. 497:8-18; 475:7-14 (Klibanov).

4. Prior Art Taught Adding Magnesium Would Improve Parenteral Tetracycline Formulations

a) CN'268 (DTX-0014)

150. It is uncontested that CN101301268 (“CN’286”) is a Chinese patent application that was published on November 12, 2008 and is prior art to the asserted patents. Pretrial Order Ex. 1 (Uncontested Facts) at 36.

151. CN'268 taught that adding magnesium to an aqueous parenteral doxycycline formulation would form a complex between the magnesium and tetracycline antibiotic that would

achieve greater solubility and stability at higher pH values, while also reducing toxicity and tissue irritability upon injection. Tr. 484:5-17 (Klibanov).

152. CN'268 was not considered during prosecution of the asserted patents and thus the Patent Office was not aware of this direct teaching that a POSA would have known in order to achieve the listed benefits. Tr. 511:20-512:1 (Klibanov); Tr. 895:6-7 (deVries).

153. CN'268 explained that its goal was to address certain limitations that had existed regarding a commercially available doxycycline formulation: (1) low concentration and (2) low administration pH that resulted in irritability when administered. DTX-0014_0003 at [0002]; Tr. 483:7-14 (Klibanov).

154. In order to achieve this goal, CN'268 taught how to create a doxycycline formulation with increased solubility, which allowed for higher concentration of the tetracycline and thus lower volume to administer the same dosage; good stability; and reduced irritability side effects. DTX-0014_0003 at [0002]; Tr. 483:15-25 (Klibanov).

155. CN'268 taught that these goals were achieved by adding magnesium ions at “higher content” to the tetracycline. DTX-0014_0005 at [0006]; Tr. 484:1-3 (Klibanov). As Dr. Klibanov explained at trial, “higher content” as used in CN'268 meant the magnesium ions were used in excess over the concentration of doxycycline. Tr. 486:3-6 (Klibanov). Neither Dr. deVries nor Dr. Friedman rebutted this. Dr. Klibanov was Defendant’s formulation expert and addressed formulation issues.

156. Specifically, CN'268 discloses parenteral formulations of the second-generation tetracycline doxycycline, and expressly explained that magnesium a “creates a complex with the doxycycline to (1) “increase the solubility and pH”, (2) “enhanc[e] the stability of the injection,” and (3) reduce “toxicity and tissue irritability.” DTX-0014_0005 at [0006].

159. Dr. Chambers further explained that CN'268 taught adding magnesium reduced toxicity and tissue irritability, which could include blood and skin impacts such as phlebitis or thrombophlebitis. Tr. 622:24-623:11 (Chambers).

161. CN'268 administered the drug to animals (finishing pigs) and reported results. Tr.
624:12-625:5 (Chambers).

163. Plaintiffs' medical expert Dr. Friedman provided no opinions regarding CN'268.
Tr. 762:25-763:4 (Friedman).

175. Gibbs further taught use of 100mg of minocycline or doxycycline in the formulation, which is the same amount used in the old Minocin IV product. DTX-0012_0002 at 2:30-32; Tr. 490:15-18 (Klibanov).

177. Gibbs taught the pH of its formulation was between 5.0-7.0, and that this pH could be achieved by adding a base as needed. DTX-0012 0003 at 3:60-4:6; Tr. 493:14-23 (Klibanov).

b) Additional Molar Ratio References

180. U.S. Patent No. 3,335,055 (“Weidenheimer”) is a U.S. Patent that issued in 1967 and is prior art to the asserted patents. Pretrial Order Ex. 1 (Uncontested Facts) at ¶ 30; DTX-0006.

181. U.S. Patent No. 3,957,980 (“Noseworthy”) is a U.S. Patent that issued on May 18, 1976 and is prior art to the asserted patents. Pretrial Order Ex. 1 (Uncontested Facts) at ¶ 31; DTX-0009.

182. U.S. Patent No. 3,846,548 (“Akazawa”) is a U.S. Patent that issued on November 5, 1974 and is prior art to the asserted patents. Pretrial Order Ex. 1 (Uncontested Facts) at ¶ 32; DTX-0008.

183. U.S. Patent No. 3,674,859 (“Beutel”) is a U.S. Patent that issued on July 4, 1972 and is prior art to the asserted patents. Pretrial Order Ex. 1 (Uncontested Facts) at ¶ 33; DTX-0007.

184. Each of Beutel, Weidenheimer, Noseworthy, and Akazawa taught use of an excess of magnesium ions over the corresponding tetracycline above 3:1 and 4:1. Tr. 494:5-15 (Klibanov). Specifically, they disclosed the following ranges:

Prior Art Reference	Molar Ratio (Mg²⁺: Tetracycline)
Beutel (DTX0007)	Up to 5:1
Weidenheimer (DTX0006)	Up to 6:1
Noseworthy (DTX0009)	Up to 8:1
Akazawa (DTX0008)	Up to 8:1

Tr. 493:25-494:15 (Klibanov, discussing DDX2015).

6. The Prior Art Taught Administration of Minocycline in Volumes below 500mL

185. The prior art taught intravenous administration of minocycline within a variety of volumes, including volumes less than 500mL.

186. As Dr. Chambers explained at trial, the old Minocin IV label itself taught administration in volumes under 500mL for pediatric patients. Tr. 626:17-22; 627:2-8 (Chambers).

193. When seeking FDA approval for the current Minocin IV label, Plaintiffs deleted Ringer's as a diluent but opted to keep Lactated Ringer's, and Plaintiffs did stability testing to justify keeping Lactated Ringer's on the label. DTX-0072_0008, & 0011

194. CN'268 taught its formulation could be prepared and administered within the pH range of 3.0-7.0, and further noted this pH range could be achieved by addition of an acid or base to adjust pH. DTX-0014_0004 at [0004]; Tr. 486:7-18 (Klibanov).

195. Gibbs taught its formulation could be prepared and administered at pH 5.0-7.0, and similarly notes its pH range could be achieved by addition of an acid or base. DTX-0012_0003 at 3:60-4:6; Tr. 493:14-23 (Klibanov).

D. Differences Between the Prior Art and the Claims at Issue

196. As Dr. Klibanov explained at trial, the prior art Minocin IV label covered all the claim elements other than adding magnesium; CN'268 and Gibbs would have motivated a person of ordinary skill to add magnesium, and optionally a base; and Plaintiffs assert that resulting claimed characteristics such as osmolality or tolerability would have been the inherent properties of such an obvious formulation. Tr. 253:10-17 (deVries); 156:22-157:11 (Friedman). Even if not inherent properties, the prior art taught keeping osmolality below 500 and taught improving tolerability by adding magnesium.

197. The prior art Minocin IV label already taught how to intravenously administer an aqueous formulation of minocycline to treat bacterial infections, and medical experts for both parties agreed the claimed formulation did not change the drug's indication. As Dr. Chambers explained, the change from the old Minocin IV formulation to the current Minocin IV formulation did not change use of the drug. Tr. 909:2-15 (Chambers). And as Plaintiffs' expert Dr. Friedman admitted, there is "no difference" in efficacy between the old Minocin IV formulation and the claimed formulations. Tr. 719:22-25 (Friedman).

211. Dr. Friedman alleged that minimizing injection volume of the old Minocin IV formulation was “important” to a POSA for critical care patients due to their unique risk of volume overload. Tr. 118:15-119:9 (Friedman).

212. Dr. deVries testified there was a motivation to decrease the volume of administration of the old Minocin IV product because “it’s a generally accepted principle that you want to have a smaller injection volume when you’re administering medication.” Tr. 842:24-843:1 (deVries).

2. A POSA would have been motivated by the teachings of CN’268 and Gibbs to address the same motivations identified by Plaintiffs by adding magnesium

213. A POSA looking to modify the prior art Minocin IV product would have looked to formulations in the prior art dealing with minocycline and related tetracyclines such as doxycycline. Tr. 482:6-11 (Klibanov).

214. Two relevant prior art references a POSA would have combined with the old Minocin IV label would have been CN’268 and Gibbs. Tr. 482:12-16; 489:8-12 (Klibanov).

215. As Dr. Klibanov explained at trial, a POSA would have been motivated to combine the CN’268 and Gibbs references with the prior art Minocin IV product label because both CN’268 and Gibbs taught techniques to improve parenteral tetracycline formulations. Tr. 500:15-23 (Klibanov); *see also* Tr. 683:1-19 (Chambers).

216. While CN’268 and Gibbs expressly disclose intramuscular formulations, injectable parenteral formulations such as intravenous and intramuscular formulations have similar considerations that would have directed a POSA to consider intramuscular references in modifying an intravenous formulation. For example, Dr. Klibanov explained that both involve aqueous and injectable formulations that differ only at the destination of the injection, so relevant characteristics are similar. Tr. 487:6-12 (Klibanov). Dr. Chambers explained intramuscular formulations

informed a POSA regarding IV tolerability because one “would expect [reduced] toxicity at the site of injection [in an IM formulation] would translate to improved tolerability if given intravenously.” Tr. 623:12-23 (Chambers).

217. A POSA further would have had a reasonable expectation of success of making the claimed minocycline-magnesium formulations and achieving any claimed features based on the prior art and knowledge and expectations of a POSA. Tr. 500:24-501:3 (Klibanov).

218. Plaintiffs’ experts Dr. deVries and Dr. Friedman each admitted that increasing pH to closer to physiological pH would have been expected to aid tolerability. Tr. 845:4-12 (deVries); Tr. 761:11-14 (Friedman).

219. Dr. Friedman testified the reduced volume was a result of “normalizing” pH, meaning that a POSA would have expected that simply permitting for adjusted pH resulted in reduced volume required for administration. Tr. 755:9-13; 121:18-23 (Friedman).

220. Dr. Friedman further testified a POSA would have known how to adjust volume, administration rate, and dosing to match the existing known therapeutically effective amount from the old Minocin IV product. Tr. 100:25-101:6 (Friedman).

221. In view of the chemical similarities between doxycycline and minocycline, as well as the teachings in the prior art that both compounds interact similarly with magnesium, a POSA would have had a reasonable expectation of success in being able to achieve the claimed formulations.

222. As Dr. Klibanov explained at trial, CN’268 recognized that existing formulations of doxycycline, a tetracycline highly similar to minocycline, could benefit from increased pH, higher concentration, and improved tolerability. Tr. 483:7-25 (Klibanov). CN’268 then expressly explained that adding magnesium to that formulation achieved these goals. Tr. 484:1-17

231. Plaintiffs' expert Dr. deVries admitted that a POSA would have known how to run experiments with varying the magnesium to minocycline molar ratio, along with other variables such as pH or concentration to assess characteristics such as solubility ratio. Tr. 889:2-9 (deVries).

232. All claims of the '802 patent require that “injection site hemolysis of red blood cells is reduced relative to intravenous administration of a composition that does not include magnesium.” PTX 1 at Cl. 1, 7, and 18.

234. Any improved tolerance including injection site hemolysis reduction, however defined, would have been obvious in view of the prior art. As Dr. Klibanov explained at trial, a POSA would have expected this result based on the teachings in CN'268 that adding magnesium

would reduce toxicity and tissue irritability of the drug. Tr. 509:1-4, 9-17 (Klibanov); DTX-0014_0005 at [0006].

5. The '105 Patent Osmolality Limitation is Either Inherent or Obvious

235. The asserted claim of the '105 patent requires that the formulation “has an osmolality of less than about 500mOsmol/kg.” PTX 2 at Cl. 27.

236. While parties disagree whether the construction of this limitation requires osmolality to be measured from a reconstituted intermediate or final administered formulation, experts from both parties agree that an osmolality is a function of the components of a formulation. Tr. 634:4-24 (Chambers); Tr. 512:11-13, 512:25-513:4 (Klibanov); Tr. 253:10-19 (deVries).

237. This osmolality limitation of the '105 patent would have been obvious in view of the prior art. As Dr. Klibanov explained at trial, a POSA would have expected this claimed property based on the prior art and standard of practice at the time. Tr. 515:16-516:9 (Klibanov); DTX-175. Plaintiffs' experts Dr. deVries and Dr. Friedman agreed that the prior art Minocin IV formulation, both the reconstituted and diluted formulations, had an osmolality of less than 500mOsmol/kg meeting this limitation and that administering formulations having osmolalities under this limit was consistent with the standard of care. Tr. 308:6-9 (deVries), 762:16-19 (Friedman). Dr. deVries also admitted that osmolality was a known and well-understood concept to a POSA. Tr. 234:14-17 (deVries).

6. The Asserted Claims are Invalid as Obvious In view of the Old Minocin IV Label, CN'268, and Gibbs

a) The '802 patent claim 1

238. Asserted claim 1 of the '802 patent is invalid as obvious in view of the prior art, particularly over the 2007 Minocin IV label in combination with CN'268 and Gibbs.

244. As explained by Dr. Klibanov, a POSA would have expected from the prior art that adding magnesium would allow a minocycline formulation to be prepared at a higher pH with improved solubility and stability. Tr. 484:5-17 (Klibanov). It was well known in the art that adding a base would result in increased pH to take advantage of this improved solubility and stability. For example, CN'268 and Gibbs both taught addition of a base to increase pH. DTX-0014_0004; Tr. 486:8-18 (Klibanov); DTX-0012_0003 at 3:60-4:6; Tr. 493:14-23 (Klibanov). Additionally, as Dr. Klibanov explained, adjusting pH with a base was well within the everyday skill set of a POSA. Tr. 469:8-14 (Klibanov).

(iii) “wherein the molar ratio of magnesium cation to minocycline is greater than about 4:1, and”

245. The claimed molar ratio range is obvious in view of the prior art and the knowledge and experience of a POSA. Tr. 508:4-9 (Klibanov).

246. Gibbs and other prior art references taught use of molar ratios of magnesium to minocycline or other tetracyclines up to 8:1, which overlaps with the claimed range, and would have motivated a POSA to prepare formulations within the molar ratio. Tr. 508:4-9 (Klibanov).

247. Alternatively, the claimed molar ratio range would have been obvious because it would have been simply a matter of routine optimization to identify a particular suitable molar ratio of magnesium to minocycline within the claimed range. Tr. 494:23-495:2 (Klibanov); Tr. 889:2-9 (deVries).

(iv) “wherein the composition has a pH that is no less than 4 and no greater than 6,”

248. Each of the 2007 Minocin IV label, CN'268, and Gibbs taught formulations prepared in substantially overlapping pH ranges and would have motivated a POSA to prepare formulations within this range with a reasonable expectation of success. Tr. 508:11-13, 18-23 (Klibanov).

251. The claimed pH range would have been obvious because it would have been simply a matter of routine optimization to adjust pH to identify a particularly suitable pH within the claimed ranges. Tr. 889:2-9 (deVries); Tr. 469:8-14 (Klibanov).

252. If this feature is actually shown to be present for infringement purposes, then it is an inherent property of the formulation and thus does not need to be established for purposes of the obviousness analysis. Tr. 229:21-24, 229:25-230:8 (deVries); Tr. 768:25-769:2 (Friedman).

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The '802 patent claim 7: The method of claim 1, wherein the composition has a pH between about 4.5 to about 5.5

254. Asserted claim 7 of the '802 patent is invalid as obvious in view of the prior art, particularly over the 2007 Minocin IV label when viewed in combination with CN'268 and Gibbs, for at least the same reasons explained above for claim 1.

255. Each of the 2007 Minocin IV label, CN'268, and Gibbs taught formulations prepared in substantially overlapping pH ranges and would have motivated a POSA to prepare formulations within this claimed pH range with a reasonable expectation of success. Tr. 510:8-11 (Klibanov).

256. The pH of the old Minocin IV product diluted in Lactated Ringer's was 4.5-6.0 and fell within this claimed range. *See* DTX-0112 0013; Tr. 480:10-17 (Klibanov).

257. To the extent Plaintiffs dispute whether this pH should refer to a reconstituted intermediate or the diluted formulation that is administered, both are obvious in view of the prior art. There is no difference between the prior art pH when Lactated Ringer's was used and only a small difference for all other diluents.

258. The claimed pH range would have been obvious because it would have been simply a matter of routine optimization to adjust pH to identify a particularly suitable pH within the claimed ranges. Tr. 889:2-9 (deVries); Tr. 469:8-14 (Klibanov).

The '802 patent claim 18: The method of claim 1, wherein the total volume of the composition administered is less than 500 ml.

259. Asserted claim 18 of the '802 patent is invalid as obvious in view of the prior art, particularly over the 2007 Minocin IV label when viewed in combination with CN'268 and Gibbs, for at least the same reasons explained above for claim 1.

the old Minocin IV product. Tr. 100:25-101:6 (Friedman). Dr. Friedman further testified the reduced volume was a result of “normalizing” pH, meaning that a POSA would have expected that simply permitting for adjusted pH resulted in reduced volume required for administration. Tr. 755:9-13, 121:18-23 (Friedman).

265. It would have been obvious to a POSA that adding magnesium to the old Minocin IV product could increase the concentration of the administered formulation and thus permit administration volumes less than 500mL such that the 2007 Minocin IV label, CN'268, and Gibbs would have motivated a POSA to prepare and use formulations within this range with a reasonable expectation of success. Tr. 510:18-511:12 (Klibanov).

d) The '105 patent claim 27

266. Asserted claim 27 of the '105 patent is invalid as obvious in view of the prior art, particularly over the 2007 Minocin IV label when viewed in combination with CN'268 and Gibbs.

267. A POSA would have been motivated to modify the product described in the prior art 2007 Minocin IV label by adding magnesium within the claimed molar ratios and pH range to obtain the use of the claimed formulation with a reasonable expectation of success. Tr. 512:2-10 (Klibanov).

(i) A method of treating a bacterial infection in a subject, wherein the method comprises administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration,

268. There is no dispute between the parties that the 2007 Minocin IV label taught these limitations. *See* Tr. 513:7-24 (Klibanov).

(ii) wherein the composition comprises an aqueous solution of a 7-dimethylaminotetracycline antibiotic and a magnesium cation,

269. The old Minocin IV label taught use of minocycline, which is a 7-dimethylaminotetracycline antibiotic, and CN'268 and Gibbs would have motivated a POSA to add a magnesium cation to the formulation with a reasonable expectation of success. Tr. 514:1-14 (Klibanov).

270. As explained by Dr. Klibanov at trial, CN'268 and Gibbs provided express motivation for a POSA to add magnesium to the prior art Minocin IV product in order to improve solubility, stability, and tolerability of the older commercial formulation. Tr. 489:1-7, 492:5-13 (Klibanov).

271. Plaintiffs' experts also admit a POSA would have been motivated to change the old Minocin IV product by increasing pH, decreasing volume (i.e. increasing concentration), and improving tolerability. Tr. 843:2-5, 842:24-843:1, 843:6-16 (deVries); Tr. 697:25-698:5, 699:3-7, 118:15-119:9, 697:25-699:7, 703:17-17 (Friedman). These are the same characteristics CN'268 reports were improved by addition of magnesium. DTX-0014_0005 at [0006]; Tr. 484:1-3 (Klibanov).

(iii) wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and

272. The claimed molar ratio range is obvious in view of the prior art and the knowledge and experience of a POSA. Tr. 514:15-17 (Klibanov).

273. Gibbs and other prior art references taught use of molar ratios of magnesium to minocycline or other tetracyclines up to 8:1, which overlaps with the claimed range, and would have motivated a POSA to prepare formulations within the claimed molar ratio range. Tr. 508:4-9 (Klibanov).

274. The claimed molar ratio range would have been obvious because it would have been simply a matter of routine optimization to identify a particular suitable molar ratio of magnesium to minocycline within the claimed range. Tr. 494:23-495:2 (Klibanov); Tr. 889:2-9 (deVries).

(iv) wherein the solution does not comprise a pharmaceutically acceptable oil,

275. Neither the 2007 Minocin IV label nor CN'268 contained a pharmaceutically acceptable oil. Tr. 514:19-25 (Klibanov).

276. It would have been obvious to a POSA that oils would not be required or useful for an intravenous minocycline formulation.

277. Moreover, as Dr. Klibanov explained, any use of oil in Gibbs was directed to the intramuscular nature of the formulation and there would be “no reason whatsoever for a person of ordinary skill in the art to consider adding an oil to an intravenous formulation of minocycline.” Tr. 492:17-493:12 (Klibanov). Dr. Chambers agreed, especially since Gibbs expressly stated why it used oil for the IM setting and why that purpose would not be applicable for the IV setting, which was separate and apart from magnesium. Tr. 619:1-620:3 (Chambers).

(v) has a pH greater than 4 and less than 7, and

278. Each of the 2007 Minocin IV label, CN'268, and Gibbs taught formulations prepared in substantially overlapping pH ranges and would have motivated a POSA to prepare formulations within this range with a reasonable expectation of success. Tr. 515:2-3, 9-13 (Klibanov).

279. The pH of the old Minocin IV product diluted in Lactated Ringer's was 4.5-6.0 and fell within this claimed range. *See* DTX-0112_0013; Tr. 480:10-17. There is no difference between that prior art example and the claimed pH. The pH of the old Minocin IV product for all other

diluents was 2.5-4.0 and also overlapped this claimed range. *Id.* There is only a small difference between that prior art example and the claimed pH.

280. To the extent Plaintiffs dispute whether this pH should refer to a reconstituted intermediate or the diluted formulation that is administered, both are obvious in view of the prior art at least because Gibbs and CN'268 each teach preparation at higher pH, and further would have taught the addition of minocycline would permit for the old Minocin IV product to be prepared at higher pH ranges by the addition of the base.

281. Alternatively, the claimed pH range would have been obvious because it would have been simply a matter of routine optimization to adjust pH to identify a particularly suitable pH within the claimed ranges. Tr. 889:2-9 (deVries); Tr. 469:8-14 (Klibanov).

(vi) has an osmolality less than about 500 mOsmol/kg.

282. Experts for both parties agree this limitation is a function of the components in a formulation, and Plaintiffs' experts admitted the value would inherently be less than 500 mL, and thus does not need to be established for purposes of the obviousness analysis. Tr. 253:10-19 (deVries).

283. This limitation is obvious in view of the prior art and expectations of a POSA due to the standard of care that required osmolality of an intravenously administered pharmaceutical formulation to be below about 500 mOsmol/kg. Tr. 515:16-516:9 (Klibanov); Tr. 308:6-9, 762:16-19 (deVries).

(vii) The method of claim 1, wherein the 7-dimethylamino-tetracycline is minocycline.

284. As explained above and by Dr. Klibanov at trial, the old Minocin IV label and Gibbs both taught use of minocycline specifically, and CN'268 and Gibbs would have motivated a POSA

to add a magnesium cation to the prior art Minocin IV formulation with a reasonable expectation of success. Tr. 514:1-14 (Klibanov).

7. Plaintiffs' Criticisms of Obviousness Lack Factual and Logical Support

285. Plaintiffs' and Dr. deVries's attempt to distinguish obviousness of prior art based on the specific tetracycline to be bound by metal cations has already been rejected by third parties such as the U.S. Patent and Trademark Office ("PTO"). DTX-0038_0009; DTX-0037_0002.

286. As Dr. Klibanov explained at trial, a POSA would readily look to prior art formulations of other tetracyclines, including doxycycline, due to the known commonalities, even though they are of course not identical compounds. Tr. 475:1-16 (Klibanov), 495:3-21, 497:8-18. Dr. Chambers also explained why a POSA would do so. Tr. 682:22-683:19.

287. That is what POSAs actually did in the prior art. For example, Gibbs used the same formulations for both doxycycline and minocycline and taught minocycline and doxycycline formulations in an essentially interchangeable manner, especially with respect to interaction with magnesium. Tr. 491:21-492:4 (Klibanov). Additionally, Berthon described "a striking similarity" between magnesium-doxycycline and magnesium-minocycline systems, again showing the relevant similarities for purposes of formulation. Tr. 884:7-17 (deVries); PTX 158 at MELINTA17578.

288. As Dr. Klibanov explained at trial, the deVries 2006 publication was a patent application that was rejected by the PTO because of prior art teaching similar tetracycline formulations with metal cations. Tr. at 499:5-500:8 (Klibanov). Specifically, Dr. deVries had argued to the PTO that prior art should not be considered for her patent because it did not disclose minocycline formulations, but the PTO rejected this argument expressly "because minocycline

shared a core structure and characteristics” with the other tetracyclines that were used in the prior art. *Id.*

289. Dr. deVries herself even relied on nearly identical methods in formulating doxycycline, minocycline, and other tetracyclines. The deVries 2006 patent application covered minocycline simultaneously with a number of other tetracyclines, an admission in itself that a POSA would have applied the same technique to many different tetracyclines. *See* PTX 134 at Cl. 1, 4.

290. The disclosures in deVries 2006 were based on an earlier patent that reported nearly identical formulations for doxycycline and not any other tetracycline. *See* DTX-0360 at claim 1. The “detailed description of the invention” section of both deVries 2006 and Dr. deVries’s doxycycline patent are virtually identical beyond the listed tetracyclines. *Compare* PTX 134 (deVries 2006) at [0016]-[0069] *with* DTX-0360 (deVries doxycycline patent) at 2:58-7:15). Dr. deVries admitted she relied on her prior doxycycline formulation experience for the minocycline project development. Tr. 883:4-7 (deVries). Dr. deVries also admitted the doxycycline and other tetracycline formulations “seem similar.” Tr. 882:12-22 (deVries).

291. Dr. deVries admitted the formulations only had to be “adjusted” because they were different compounds, Tr. 879:23-880:2, but that is again routine experimentation. In fact, Dr. deVries agreed a POSA would know how to vary characteristics such as molar ratios or pH to assess characteristics such as solubility. Tr. 889:2-9 (deVries).

292. Dr. Friedman’s allegation that Lactated Ringer’s was not actually used in practice was unsupported by evidence. Tr. 727:20-24 (Friedman). It also contradicted the FDA-approved prior art Minocin IV label. DTX-0112_0013. In fact, Dr. Friedman admitted that it was “known that you could use Lactated Ringer’s to dilute the formulation.” Tr. 727:14-19 (Friedman).

295. As Dr. Klibanov explained, a POSA would have understood CN'268 to report that magnesium and not any other excipient was increasing solubility, stability, and tolerability of the tetracycline formulation. Tr. 488:19-25 (Klibanov).

297. As Dr. Chambers explained at trial, the CN'268 reference specifically disclosed tissue toxicity which includes the same blood toxicity issues discussed in this case. Tr. 622:20-623:8 (Chambers). Plaintiffs did not rebut this fact.

299. As Dr. Klibanov explained, Gibbs taught minocycline formulations, in addition to doxycycline formulations in an essentially interchangeable manner, especially with respect to interaction with magnesium. Tr. 491:1-492:4 (Klibanov).

300. Gibbs also explained that its formulation required formation of metal complexes between minocycline and magnesium, and taught that molar ratios of up to 8:1 would be suitable for this purpose. Tr. 491:16-492:13 (Klibanov).

301. Regardless, a POSA would have been able to identify a suitable molar ratio based on routine experimentation, and nothing in the prior art would have discouraged a POSA from doing so. Tr. 494:23-495:2 (Klibanov); 889:2-9 (deVries).

302. Contrary to Plaintiffs’ allegations, the prior art did not teach “necessity” of any other stabilizing or solubility agents for modifying the prior art Minocin IV product.

303. A POSA would not have expected any additional excipients in Gibbs to be required for modification of the old Minocin IV product. For example, as Dr. deVries admitted, Gibbs described the use of antioxidant as “preferably added,” which Dr. deVries admitted meant the excipient was optional, and not necessary to the formulation. Tr. 895:23-896:5 (deVries). Additionally, as Dr. Klibanov and Dr. Chambers explained, a POSA would know that oils used in Gibbs would not be useful for intravenous administration and would have excluded it for that reason. Tr. 492:17-493:12 (Klibanov); 620:2-621:14 (Chambers).

304. A POSA would not have expected any additional excipients in CN'268 to be required for modification of the old Minocin IV product. For example, CN'268 expressly attributed solubility, stability, and tolerability benefits to the magnesium excipient only. Tr. 488:19-25 (Klibanov). Also, as Dr. deVries admitted, CN'268 specifically reported the function of its dissolvent for storage at a particular low temperature. Tr. 895:3-7 (deVries); DTX-0014_0005 at [0006](2). In contrast, the old Minocin IV product was stored only at room temperature. Tr. 481:11-19 (Klibanov); DTX-0112 0013.

305. As Dr. Klibanov explained at trial, even though a POSA would consider other excipients such as antioxidants, a POSA would not expect it to be necessary for modification of the old Minocin IV. Tr. 488:5-18 (Klibanov). Regardless of any additional excipients used in the prior art such as antioxidants could have been separately “helpful” for other reasons, Tr. 540:25-541:6 (Klibanov), there is no reason they would have been considered necessary by a POSA for the intravenous minocycline formulation at hand.

306. Dr. Klibanov explained a POSA “would be cognizant that you only add excipients if they’re needed, and therefore if for an intravenous formulation of minocycline those [other stabilizing or solubilizing] excipients are not needed, which they are not, then they would not be added.” Tr. 491:6-10 (Klibanov). Dr. deVries in turn admitted that a guiding principle for formulators at the time, as reported in Broadhead, was to “keep it simple”, which she agreed meant “avoid excipients that you don’t need.” Tr. 856:1-14 (deVries).

307. Asserted claim 27 of the ’105 patent does not exclude antioxidants. PTX 2 at Cl. 27.

308. Plaintiffs’ argument that a POSA would not extrapolate from intramuscular to intravenous because intramuscular formulations *can* accommodate suspended solid particles (*i.e.* can be aqueous solutions or not) while intravenous formulations cannot (they are aqueous) is refuted by trial testimony.

309. There is no reason a POSA would not extrapolate from prior art teaching intramuscular formulations. As Dr. Klibanov and Dr. Chambers explained at trial, parenteral formulations such as intravenous and intramuscular formulation have similar considerations that would have directed a POSA to consider intramuscular references in modifying an intravenous formulation. For example, Dr. Klibanov explained that both are aqueous formulations that differ

only at the destination of the injection, so relevant characteristics are similar. Tr. 487:6-12 (Klibanov). He also explained it is a formulator's job and routine practice to figure out how to adjust excipients based on known characteristics, including route of administration. Tr. 465:8-24 (Klibanov). Additionally, Dr. Chambers explained intramuscular formulations are informative regarding tolerability of similar intravenous formulations and a POSA "would expect [reduced] toxicity at the site of injection [in an intramuscular formulation] would translate to improved tolerability if given intravenously." Tr. 623:12-23 (Chambers).

310. There is no dispute that there were prior art intramuscular formulations, such as CN'268, that were in fact aqueous solutions. *See, e.g.*, Tr. 486:25-487:5 (Klibanov).

311. A POSA would know how to consider intramuscular formulations and exclude unnecessary ingredients for the intravenous purpose. *See, e.g.*, Tr. 492:17-493:12 (Klibanov); 620:2-621:14 (Chambers).

312. Dr. deVries's lack of experience with intravenous or intramuscular formulations prevents her from being able to present credible allegations regarding what a POSA would have expected. Tr. 851:18-852:6; 873:15-16 (deVries). Moreover, Plaintiffs' allegation is inconsistent with Dr. deVries's testimony that all "parenteral" formulations were pertinent, including her only experience with non-oral minocycline in a "foam" approach. Tr. 199:3-21 (deVries).

E. There Are No Objective Indicia Weighing Against Obviousness

313. Plaintiffs rely on comparison to the new Minocin IV product as an embodiment of the claims for purposes of these objective indicia. Plaintiffs did not show that the old Minocin IV was the closest prior art, since the old Minocin IV did not have magnesium in it while other formulations, such as those disclosed in Isbister, did. *See* Tr. 421:1-19 (Griffith describing DTX-0013).

316. Plaintiffs have not attempted to connect any of the secondary considerations to the osmolality requirement of the '105 patent.

317. Plaintiffs cannot show any long-felt need relevant to the obviousness analysis, let alone strong enough to overcome obviousness in this case.

318. Plaintiffs do not cite any objective evidence stating any shortcomings with the prior art Minocin IV product.

320. Dr. Friedman provided no evidence of an articulated and identified problem in the prior art.

321. Mr. Griffith testified only on specific warnings and side effects listed on the old Minocin IV label, which he admitted are *still* present in the current Minocin IV label. *See, e.g.*, Tr. 329:6-331:18 (Griffith).

322. Mr. Griffith does not meet either party's definition of a POSA. Tr. 381:10-382:3 (Griffith).

323. Plaintiffs cite to prior art reference Klein, but that does not reference the old Minocin IV formulation at all. *See* PTX 182.

324. Plaintiffs cite to prior art reference Sweetana, but that does nothing more than list the Minocin IV product with reconstituted pH and other formulation characteristics among dozens of drugs in a table. PTX 233 at MELINTA017409.

325. Broadhead reported formulations administered at pH 2-12 generally "can be tolerated" "in practice." Tr. 853:16-23 (deVries); PTX 225 at MELINTA017609.

326. The only prior art containing tolerability data for the old Minocin IV product showed there were no incidences of "injection site hemolysis," listed one incident of phlebitis (not even attributed to the drug), and four incidences (less than 4%) of thrombophlebitis which were considered "minor." PTX 164 at MELINTA017251 (Clark); Tr. 437:9-438:24 (Friedman).

b) There is virtually no change between how the old and new Minocin IV products are used

327. Any differences between the old and new Minocin IV product are minimal.

328. Plaintiffs' expert Dr. Friedman admits there's "no difference" between the efficacy of the previous minocycline formulation and the efficacy of the current minocycline formulations. Tr. 719:22-25 (Friedman).

329. As Dr. Chambers testified, the new formulation did not change the use of the drug. Tr. 908:14-21 (Chambers).

2. Plaintiffs Have Not Established Any Surprising or Unexpected Results by the Claimed Formulations

349. Additionally, Gibbs taught formulations of minocycline with magnesium at pH 5.0 and 7.0, and CN'268 taught similar formulations of doxycycline with magnesium at pH 3.0-7.0. DTX-0012_0003 at 3:60-4:6; Tr. 493:14-23 (Klibanov); DTX-0014_0004; Tr. 486:8-18 (Klibanov).

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367. deVries 2006 is a patent publication directed to oral formulations—not parenteral formulations. Tr. 875:8-13 (deVries).

369. deVries 2006 taught aqueous solutions of minocycline and magnesium could be prepared within the claimed pH ranges. *See, e.g.*, DTX-0010 at [0070] (reporting suspension does not occur until “final pH in the range of from about 5 to less than about 8”).

371. Barringer does not teach away from the claimed formulations. Barringer discloses an experiment of a 2:1 molar ratio of magnesium to minocycline at a single high pH (6.5), which has no nexus to the scope of what is claimed. All claims start at pH 4.0 to 4.5 and require higher molar ratios than used in the Barringer experiment. Tr. 919:13-16 (Klibanov).

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375. Allen does not teach away from the claimed formulations. Dr. deVries’s citation to a statement in Allen that she in turn reported as citing to Barringer and providing the “the same message” does not teach away for the same reasons as Barringer. Tr. 790:12-19 (deVries).

377. Berthon does not teach away from the claimed formulations. Dr. deVries cited to Berthon showing minocycline and magnesium would see precipitation at increasing pH, but not specific conditions from Berthon relating to the patents.

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V. INVALIDITY UNDER SECTION 112

385. Plaintiffs sought and obtained claims that are broader than the specifications’ disclosures and do not inform a POSA with reasonable certainty as to their boundaries.

A. “Injection Site Hemolysis” Cannot Be Measured

386. The asserted claims of the '802 patent all require that “injection site hemolysis” is reduced as compared to a minocycline formulation without magnesium. PTX 1, Cl. 1, 7, and 18.

387. The '802 patent fails to define “injection site hemolysis” and it is undisputed that it also fails to disclose how to measure injection site hemolysis. Tr. 505:6-7 (Klibanov); 596:24-597:8 (Chambers); 742:12-743:2 (Friedman).

388. Nexus's expert, Dr. Chambers, explained that there is no way to know or measure the extent of hemolysis at the point the drug enters the bloodstream. Tr. 679:24-680:1.

389. Plaintiffs' expert, Dr. Friedman, admitted that he has never personally observed injection site hemolysis. Tr. 743:3-744:12. He also admitted that there is no disclosure of where in the vein injection site hemolysis starts and stops, or that the '802 patent teaches how to measure the rate or extent of hemolysis anywhere in the bloodstream. Tr. 742:12-19, 742:23-743:2 (Friedman).

390. “Injection site hemolysis” is not a term that a POSA would readily understand because it is not defined in the medical field. Tr. 595:2-11, 596:17-20 (Chambers).

391. A POSA would also not understand other tolerability issues to serve as a proxy for “injection site hemolysis” and there is no understanding of a causal link between “injection site hemolysis” and tolerability issues such as phlebitis. Tr. 597:9-17 (Chambers).

392. While the '802 patent describes hemolysis, and a POSA understands that term, the patent specification provides no guidance regarding “injection site hemolysis” and a POSA would be unfamiliar with that alleged phenomenon. Tr. 588:22-589:7 (Chambers). Accordingly,

Plaintiffs rely on references to the patent specification pointing to “hemolysis” rather than “injection site hemolysis.” D.I. 249 at 7-8 (citing FOF ¶¶ 65-68).

all require intravenous infusion of minocycline. *See, e.g.*, PTX 1 at Cl. 1. Mr. Griffith, a named inventor, testified that there was no testing using an IV infusion with the current minocycline formulation. Tr. 409:14-19, 410:11-20, 410:24-411:3 (Griffith).

403. It is undisputed that the rabbit red blood cells relied upon by Plaintiffs are highly sensitive and conducted in conditions that are “highly artificial.” Tr. 598:11-23 (Chambers); 837:8-13, 859:18-860:8 (Dr. deVries admitting that rabbit red blood cell tests are highly sensitive and too much exposure in the test conditions can result in “overestimation of the damage”).

404. Plaintiffs’ expert Dr. Friedman alleged that a POSA would understand there was a reduction in injection site hemolysis because of a reduction in phlebitis. Tr. 114:4-115:2, 115:19-116:16 (Friedman). However, Plaintiffs’ other expert, as well as Dr. Chambers, testified that hemolysis and phlebitis are distinct. Tr. 860:12-861:17 (Dr. deVries relying on the Broadhead reference to conclude no causal link); 597:9-17 (Dr. Chambers testifying consistently that there is “no theoretical basis or proven basis” linking hemolysis to phlebitis).

405. It is undisputed that there is no way to observe or quantitatively measure injection site hemolysis. Tr. 679:24-680:1 (Chambers); Tr. 743:11-744:12 (Friedman).

406. The ’802 patent also failed to disclose any methods for measuring injection site hemolysis. Tr. 742:12-19, 742:23-743:2 (Friedman); 679:24-680:1 (Chambers).

407. Plaintiffs’ expert admitted that a study to prove a reduction in injection site hemolysis would be cost prohibitive. Tr. 164:5-11 (Friedman).

C. The pH Limitations Lack Adequate Written Description and Are Not Enabled

408. Claims 1 and 18 of the ’802 patent require the formulation to be an aqueous solution of minocycline where magnesium to minocycline ratios are greater than 4:1 and the pH is between 4 and 6. PTX 1, Cl. 1, 18. Claim 27 of the ’105 patent also requires an aqueous solution, a ratio of greater than 3:1, and a pH of between 4 and 7. PTX 2, Cl. 1, 27.

D. Claim 18 of the '802 Patent Lacks Adequate Written Description and Is Not Enabled

418. Plaintiffs' physician expert Dr. Friedman conceded that a clinician would never use very low volumes because that would affect the therapeutic effectiveness of the drug and could be toxic to the patient. Tr. 714:8-18 (Friedman).

420. The specification shows no clinical trials or administration of any volume. Example 13 in the '802 patent shows how to make one volume with minocycline, 10 mL. PTX 1 at 38:6-43. The patent does not show how to use that one volume, or any administration examples.

422. Dr. Chambers pointed out there is similarly no data for the full range of administration volumes claimed. Tr. 614:15-20 (Chambers).

E. The Claimed Osmolality Range Lacks Written Description and Lacks Enablement

423. Claim 27 of the '105 patent requires the osmolality of the claimed "composition" must be less than 500 mOsmol/kg, including the full range of 0-500 mOsmol/kg. PTX 2, Cl. 27; Tr. 610:6-9 (Chambers).

424. The '105 patent reports only two actual osmolalities in the specification. PTX 2 at 39:6-16, 39:24-34. Both formulations with a reported osmolality with 275-375 mOsmol/kg and 150-250 mOsmol/kg, respectively. *Id.*; Tr. 833:13-19 (deVries).

425. However, the patent fails to show other actual osmolalities or that lower osmolalities are operable. Nexus's expert, Dr. Chambers, explained that very low osmolalities towards zero cause harmful effects. Tr. 610:10-611:3 (Chambers).

426. Dr. Friedman agreed that the blood's osmolality is "around 300 milliosmols per kilogram" and "to minimize the stress on the body, it is desirable to have the osmolality in the vicinity of this physiological osmolality range." Tr. 470:4-8 (Friedman).

427. Dr. Friedman further testified that osmolalities that are too low risk tissue damage, but that a POSA would know there is a lower limit. Tr. 716:20-717:8 (Friedman). Importantly, Dr. Friedman never testified what the lower limit is, nor that the '105 patent discloses it.

PROPOSED CONCLUSIONS OF LAW

I. CLAIM CONSTRUCTION

A. Legal Standard

1. Claim construction is a question of law; applying the claims once construed for infringement is a question of fact. *Markman v. Westview*, 517 U.S. 370, 384-385 (1996).

2. Claim construction is a critical stage with a separate phase of litigation devoted to its resolution. The Supreme Court’s seminal *Markman v. Westview* decision made clear that claims construction is a question of law, and applying the claims once construed is a question of fact. *Id.*

3. This District has provided Local Patent Rules consistent with the Supreme Court's decision to hold so-called *Markman* briefings and hearing in advance of the close of fact discovery and prior to the commencement of expert discovery. *See* L. Pat. R. 4.1-4.3.

4. “The name of the game is the claim.” *In re Hiniker Co.*, 150 F.3d 1362, 1369 (Fed. Cir. 1998).

5. “It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2012) (internal quotation marks omitted).

6. “[W]ords in a claim are generally given their ordinary and customary meaning”. *Vitrionics Corp. v. Conceptronic Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Phillips*, 415 F.3d at 1312. “[T]he ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words.” *Phillips*, 415 F.3d at 1314.

9. The starting point of any claim construction is to “look at the words of the claims themselves, both asserted and non-asserted, to define the scope of the patented invention. *Vitronics Corp.*, 90 F.3d at 1582 (citation omitted).

11. Where the plain and ordinary meaning of a term within the claim is clear, no further construction is required. *See, e.g., Phillips*, 415 F.3d at 1314 (“[T]he ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words.”). “Where, as here, the claim is susceptible to only one reasonable construction...[the Court] must construe the claims based on the patentee’s version of the claim as he himself drafted it.” *Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) (*quoting Process Control Corp. v. Hydrexclaim Corp.*, 190 F.3d 1350, 1357 (Fed. Cir. 1999)).

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inventor acted as his own lexicographer or intentionally disclaimed or disavowed claim scope.” *Aventis Pharms., Inc. v. Amino Chems. Ltd.*, 715 F.3d 1363, 1373 (Fed. Cir. 2013). Importantly, courts “do not read limitations from the specification into the claims; we do not redefine words.” *Thorner*, 669 F.3d at 1366. Extrinsic evidence is the last resort and cannot contradict the clear intrinsic evidence. *Immunex Corp. v. Sanofi-Aventis U.S. LLC*, 977 F.3d 1212, 1222 (Fed. Cir. 2020).

13. “Where the specification does not *require* a limitation, that limitation should not be read from the specification into the claims.” *E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430, 1433 (Fed. Cir. 1988) (emphasis in original) (internal quotation omitted). “No matter how great the temptations...courts do not rework claims. They only interpret them.” *Id.* (quoting *Autogrio Co. of Am. v. US*, 384 F.2d 391, 395-96 (Ct. Cl. 1967)).

14. Claims are to be construed based on the patent itself as issued, and not subsequent litigation-driven efforts by the patentee. For example, claims must be construed “without the objective of capturing or excluding the accused device.” *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1324 (Fed. Cir. 2009). Similarly, “claim construction...focuses on the recited limitations of the *claims*, not on the features of a commercial embodiment of the invention.” *Myco*, 955 F. 3d at 15 (emphasis in original).

15. A claim term must be construed consistently throughout all the claims. *See CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1159 (Fed. Cir. 1997).

16. Additionally, courts cannot rewrite claims to save them from invalidity. *See Abbott Labs. v. Dey, L.P.*, 110 F. Supp. 2d 667, 674 (N.D. Ill. 2000) (citing *K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1364-65 (Fed. Cir. 1999) (“Courts do not rewrite claims; instead, we give effect to the terms chosen by the patentee.”)).

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17. The claim term “administering” should be construed consistent with its plain and

18. Plaintiffs’ proposed construction for “administering” to include the two steps of

2. “Composition”

19. The claim term “composition” should be construed consistent with its plain and

20. Plaintiffs' proposed construction for "composition" to refer to an intermediate

3. “Consists of” and “Consisting Of”

21. It is well established that the terms “consists of” of “consisting of” “creates a very

24. Plaintiffs’ argument that the plain language should be ignored to allow for additional components within the formulation relies upon how a commercial product is used, which is not permitted under the law. *Myco*, 955 F. 3d at 15 (“claim construction...focuses on the recited limitations of the *claims*, not on the features of a commercial embodiment of the invention.” (emphasis in original)); *AFG Indus.*, 239 F.3d at 1245 (“‘closed’ transition phrases such as ‘consisting of’ are understood to exclude any elements, steps, or ingredients not specified in the claim”).

25. Plaintiffs raised the construction of “subject” during trial but did not provide a construction or argument in its opening brief. The claim term “subject” should be construed consistent with its plain and ordinary meaning, which is not limited to humans.

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5. “Does Not Include Magnesium”

27. The claim term “does not include magnesium” should be construed consistent with its plain and ordinary meaning, which is a comparator formulation that does not include magnesium.

28. Plaintiffs’ proposed construction to expand the claim language to further include formulations that do not include other metal cations must be rejected because it is inconsistent with the words of the claims themselves and there is no evidence in the specification that the inventor acted as his own lexicographer. *See Vitronics*, 90 F.3d at 1582. The Court, therefore, declines to re-write the claims to add language that “does not include magnesium” excludes not only magnesium but other metal cations as well.

II. NON-INFRINGEMENT

A. Legal Standards

29. Nexus may avoid liability by either a finding of invalidity or non-infringement, whereas Plaintiffs must satisfy both. *See, e.g., Commil USA, LLC v. Cisco Systems, Inc.*, 575 U.S. 632, 637 (2015) (explaining that it is “axiomatic that one cannot infringe an invalid patent”).

30. It is Plaintiffs’ burden to prove infringement of each asserted claim by a preponderance of the evidence. *Takeda Pharm. Co. v. Teva Pharm. USA, Inc.*, 668 F. Supp.2d 614, 619 (D. Del. 2009) (“The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence.”).

31. In order to show infringement, Plaintiffs must show Nexus’s accused product will meet each and every limitation of the asserted claims. “If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law.” *Bayer AG v. Elan Pharma. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000); *see also MicroStrategy Inc. v. Bus. Objects, S.A.*, 429 F.3d 1344, 1352 (Fed. Cir. 2005) (“If, however, even one claim limitation is missing or

33. A method claim is not infringed unless all of the steps are carried out. *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 921 (2014).

35. It is legal error for a court to compare the accused product or process with a patentee's commercial embodiment instead of the claims themselves within the infringement analysis. *Zenith Labs. v. Bristol-Myers Squibb*, 19 F.3d 1418, 1423 (Fed. Cir. 1994) ("As we have repeatedly said, it is error for a court to compare in its infringement analysis the accused product or process with the patentee's commercial embodiment or other version of the product or process; the only proper comparison is with the claims of the patent.").

36. For induced infringement, Plaintiffs must show that Nexus actively encouraged infringement, knowing that the acts it induced constitute patent infringement, and that the encouraging acts actually resulted in direct patent infringement. “The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not

sufficient for inducement.” *Takeda*, 785 F.3d at 631. To prove induced infringement, Plaintiffs must show more than the “mere knowledge of possible infringement” but rather “specific intent and action to induce infringement must be proven.” *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363- 64 (Fed. Cir. 2003).

37. “It is not enough to simply intend to induce the infringing acts” as Plaintiffs must specifically prove inducing “actual infringement.” *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1331-32 (Fed. Cir. 2010). Selling a product even with knowledge that it could be applied to infringe does not prove specific intent to induce infringement. *Warner-Lambert*, 316 F.3d at 1364 (“[I]f a physician, without inducement by Apotex, prescribes a use of gabapentin in an infringing manner, Apotex’s knowledge is legally irrelevant.”); *see also Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1319-20 (Fed. Cir. 2012) (affirming non-infringement where claim requirements “contrary to the contents of the FDA-approved label”); *Takeda*, 785 F.3d at 631 (affirming non-infringement because “label must encourage, recommend, or promote infringement” beyond knowledge of potentially infringing uses).

38. In pharmaceutical patent cases, a patentee demonstrates inducement by proving the ANDA applicant “has or will promote or encourage doctors to infringe the [] method patent,” through statements made in the proposed package insert. *Warner-Lambert*, 316 F.3d at 1364; *see also HZNP Medicines LLC v. Actavis Laboratories UT, Inc.*, 940 F.3d 680, 699 (Fed. Cir. 2019).

39. “The question is not...whether a user following the instructions may end up using the device in an infringing way. Rather, it is whether [the] instructions teach an infringing use of the device.” *Vita-Mix Corp.*, 581 F.3d at 1329 n.2.

40. The product label's indifference towards a claim requirement is insufficient to establish induced infringement. *See, e.g., Shire LLC v. Amneal Pharms. LLC*, No. 11-3781, 2014 WL 2861430, at *4-5 (D.N.J. June 24, 2014).

2. Contributory

41. For contributory infringement, Plaintiffs must show that Nexus will sell a product “for use in a practicing a patented process” with knowledge the product was “made or especially adapted for use in an infringement” and without “substantial noninfringing use.” 35 U.S.C. § 271(c).

42. Contributory infringement, like inducement, still requires proof of actual direct infringement, because direct infringement cannot be assumed on “mere inferences” alone. *DSU Medical Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1304-1305 (Fed. Cir. 2006) (affirming non-infringement judgment for needle shield sold in open configuration without proof it was ever in fact closed).

43. Knowledge of infringement means not just knowing about “the patent and of the relevant acts,” but that the product use “was both patented *and infringing*.” *Fujitsu Ltd.*, 620 F.3d at 1330 (emphasis added).

44. The Supreme Court confirmed that “[l]ike induced infringement, contributory infringement requires knowledge of the patent in suit and knowledge of patent infringement.” *Commil*, 575 U.S. at 639.

45. Any reasonable use is a substantial use, even if not commercially viable. “Non-infringing uses are substantial when they are not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental.” *Vita-Mix*, 581 F.3d at 1324, 1327.

B. Plaintiffs Fail to Prove Infringement of the '105 Patent Asserted Claims

46. Plaintiffs only assert indirect infringement, and thus must prove that there is **both** (a) direct infringement by physicians of every limitation of claim 27 of the '105 patent and (b) Nexus is indirectly liable for that infringement through inducement or contributory infringement. *Takeda*, 785 F.3d at 634 (“direct infringement [] is a prerequisite for indirect infringement”). Plaintiffs bear the burden of proving the direct and indirect infringement of every limitation by a preponderance of the evidence. *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1535 (Fed. Cir. 1991).

47. Plaintiffs did not show direct infringement because they failed to show that Nexus’s ANDA product has an osmolality of less than about 500 mOsmol/kg. Plaintiffs merely rely on the fact that Nexus’s product and their product have the same formulation, but introduced no evidence as to what Nexus’s product’s properties are. The Federal Circuit has made clear that the only proper comparison for infringement is the accused product or process with the claims of the patent. *Zenith Labs.*, 19 F.3d at 1423.

48. As described above, Plaintiffs failed to prove direct infringement of the osmolality claim limitation, thus, as a matter of law, Nexus cannot be held liable for indirect infringement. *Takeda*, 785 F.3d at 634.

49. Even if Plaintiffs had sufficiently shown direct infringement, Plaintiffs failed to sufficiently show evidence of indirect infringement. Plaintiffs never showed that Nexus knows the osmolality of its formulation, in the reconstituted intermediate or in the diluted IV bag, much less that Nexus knew it infringed the '105 patent. *See, e.g., Fujitsu*, 620 F.3d at 1330.

50. Plaintiffs also failed to show that there are no substantial non-infringing uses, as required by the statute for contributory infringement. 35 U.S.C. § 271(c).

53. Plaintiffs did not show that third parties will directly infringe claim 27 of the '105 patent.

55. Plaintiffs did not meet their burden to show that Nexus can be liable for contributory infringement of claim 27 of the '105 patent under 35 U.S.C. § 271(c).

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59. If Nexus was aware of the alleged reduction in injection site hemolysis, mere knowledge of results is not legally sufficient to establish inducement without a labeled instruction related to the claims themselves. *Bayer*, 676 F.3d at 1319-20.

61. Similarly, the Federal Circuit has also held that, like here, where a drug has a prior art use and an asserted patent uses the same drug for an addition feature, the patents “do not claim the [prior art] use” because “[t]hat use, like the drug itself, is unpatented and in the public domain.” *Allergan, Inc. v. Alcon Labs*, 324 F.3d 1322, 1327 (Fed. Cir. 2003).

62. As described above, Plaintiffs selected the use of the close-ended “consisting of” and “consists of” language for claim 1 of the ’802 patent. Thus, Plaintiffs ensured that the formulation to be administered must only have the three listed components: water with minocycline, magnesium, and a base.

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steps, then there cannot be literal infringement as a matter of law. *DeMarini Sports*, 239 F.3d at 1331; *Wavetronix*, 573 F.3d at 1359; *Limelight Networks*, 572 U.S. at 921.

64. Because claim 1 is not infringed, claims 7 and 18 also cannot be infringed, because it is a “fundamental principle of patent law” that “dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed.” *Jenneric/Pentron, Inc. v. Dillon Co., Inc.*, 205 F.3d 1377, 1383 (Fed. Cir. 2000) (quotations omitted).

III. OBVIOUSNESS

A. Legal Standards

65. A patent or patent claim is invalid for obviousness under 35 U.S.C. § 103 “when the difference between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a [POSA] to which said subject matter pertains.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *see also* 35 U.S.C. § 103.

66. The test is the same for infringement and invalidity. “A century-old axiom of patent law holds that a product “which would literally infringe if later in time anticipated if earlier.”” *Upsher-Smith Labs, Inc. v. PAMLAB, LLC*, 412 F.3d 1319, 1322 (Fed. Cir. 2005).

67. Obviousness is a question of law based on underlying facts including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the pertinent art, (3) the differences between the prior art and the claims at issue, and (4) secondary considerations. *Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1097-98 (Fed. Cir. 2015); *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1346-47 (Fed. Cir. 2009).

68. Based on these factual inquiries, the Court must determine, as a matter of law, whether the claimed subject matter as a whole would have been obvious to one of ordinary skill in

75. Prior art references may be combined with the knowledge and/or experience of a POSA to “fill in the gap when limitations of the claimed invention are not specifically found in the prior art.” *Belden Techs., Inc. v. Superior Essex Commc’ns LP*, 802 F.Supp.2d 555, 563 (D. Del. 2011) (citing *Purdue Pharma Products L.P. v. Par Pharma., Inc.*, 642 F.Supp.2d 326, 360 (D. Del. 2009); *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013) (“[T]he knowledge of such an artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious.”)).

76. There is no requirement for an express teaching, suggestion, or motivation (an abrogated “TSM test”)—although where available that can make obviousness even easier to show—since “any need or problem known in the field” can provide a reason to combine obvious elements. *KSR*, 550 U.S. at 418-420.

77. “Obviousness does not require absolute predictability of success;” rather, “[a]ll that is required is a reasonable expectation of success” in making the invention via the combination. *Medichem, S.A. v. Rolabe, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (citation omitted); *see also Duramed Pharm., Inc. v. Watson Labs., Inc.*, 413 Fed. Appx. 289, 294 (Fed. Cir. 2011) (“There is no requirement that a teaching in the prior art be scientifically tested or even guaranteed success before providing a reason to combine. Rather, it is sufficient that one of ordinary skill in the art would perceive from the prior art a reasonable likelihood of success.”) (citations omitted). Unlike infringement, which requires proving by a preponderance of evidence that an accused product actually meets the claim elements, obviousness requires a higher clear and convincing standard of proof but a lower threshold to show a “reasonable expectation of success.”

78. A POSA “is also a person of ordinary creativity, not an automaton.” *KSR*, 550 U.S. at 421. “[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple

patents together like pieces of a puzzle.” *Id.* at 420. Thus, “obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007); *see also In re O’Farrell*, 853 F.2d 894, 904 (Fed. Cir. 1988) (“For obviousness under § 103, all that is required is a reasonable expectation of success.”); *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013).

79. Issues to be analyzed through the lens of a POSA, such as obviousness, or else the testifying witnesses' opinions have little weight. *Kyocera Senco Indus. Tools. Inc. v. ITC*, 22 F.4th 1369 (Fed. Cir. 2022).

80. Anticipation (35 U.S.C. § 102) is distinct from obviousness (35 U.S.C. § 103) since for obviousness, unlike anticipation, there is no requirement that all of the claim elements be found within one reference. *Compare* 35 U.S.C. § 102 *with* 35 U.S.C. § 103.

81. A determination that a claimed reference would be obvious “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a [POSA] would employ.” *KSR*, 550 U.S. at 418.

82. For example, “if a technique has been used to improve one device, and a [POSA] would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person’s skill.” *KSR*, 550 U.S. at 401.

83. Similarly, “[w]hen the prior art provides the means of making the invention and predicts the results, and the patentee merely verifies the expectation through ‘routine testing,’ the claims are obvious.” *Purdue Pharma*, 642 F. Supp.2d at 368 (citing *Pfizer*, 480 F.3d at 1367).

84. Also, “[w]hen compounds share significant structural and functional similarity, those compounds are likely to share other properties, including optimal formulation for long-term stability.” *Valeant Pharms. v. Mylan Pharms.*, 955 F.3d 25, 32-33 (Fed. Cir. 2020).

85. Further, “[a] prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.” *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (citing *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997)); *see also UCB v. Actavis*, 65 F.4th 679, 687 (Fed. Cir. 2023); *In re Woodruff*, 919 F.2d 1575, 1578 (CCPA 1990); *In re Malagari*, 499 F.2d 1297, 1303 (CCPA 1974)).

86. Routine optimization of an otherwise obvious embodiment is not sufficient to avoid obviousness. *In re Aller*, 220 F.2d 454, 456 (CCPA 1955) (“it is not inventive to discover the optimum or workable ranges by routine experimentation”).

87. “[I]nherency may supply a missing claim limitation in an obviousness analysis.” *Par Pharm., Inc. v. TWI Pharm. Inc.*, 773 F.3d 1186, 1194-95 (Fed. Cir. 2014); *see also, e.g., Allergan, Inc.*, 726 F.3d at 1294 n.1.

88. An element is inherent for purposes of the obviousness analysis “when the limitation at issue is the ‘natural result’ of the combination of prior art elements.” *Par*, 773 F.3d at 1195; *see also In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012).

89. As the Federal Circuit recently reiterated, “[i]t is well-settled that the inclusion of an inherent, but undisclosed, property of a composition does not render a claim to the composition nonobvious.” *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020). If a property is inherent, “there is no question of a reasonable expectation of success in achieving it.” *Id.*; *see also Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985).

90. Adding an inherent property to an obvious formulation does not make the formulation non-obvious because identifying a property associated with an obvious formulation—even if one is the first to identify that property—is not regarded as an invention. *Atlas Powder Co. v. Hanex Prods., Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999); *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (“An obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations. To hold otherwise would allow any formation—no matter how obvious—to become patentable merely by testing and claiming an inherent property.”); *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (inherency appropriate in obviousness context where it concerns a “property that is necessarily present”); *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) (“Even if no prior art of record explicitly discusses the [limitation], the... application itself instructs that [the limitation] is not an additional requirement imposed by the claims on the [claimed invention], but rather a property necessarily present in the [claimed invention].”).

91. Even where a patent challenger relies on the same prior art considered during examination, nothing more than clear and convincing evidence is required in order to prove obviousness. *Intercontinental Great Brands LLC v. Kellogg N.A. Co.*, 869 F.3d 1336, 1350-51 (Fed. Cir. 2017). Regardless, there is no “enhanced burden” on a patent challenger where the Patent Office did not previously assess the same argument or combination. *Id.*

92. When a prior art reference is not relied upon by the Patent Office for an obviousness rejection “the alleged infringer’s burden may be more easily carried because of this additional reference.” *SIBIA Neurosciences, Inc. v. Cadus Pharma. Corp.*, 225 F.3d 1349, 1355-56 (Fed. Cir. 2000) (citing *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1569 (Fed. Cir. 1996)).

93. In its obviousness analysis, a court also considers secondary considerations of nonobviousness, also known as objective indicia of non-obviousness. *See KSR*, 550 U.S. at 406.

B. Secondary Considerations

94. Secondary considerations of nonobviousness “can include evidence of commercial success, long felt but unsolved needs, and failure of others, as well as unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans before the invention.” *Aventis Pharma S.A. v. Hospira Inc.*, 743 F.Supp.2d 305, 344 (D. Del. 2010). “Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness.” *Iron Grip Baseball Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004).

95. Plaintiffs bear the burden of production with respect to evidence of any alleged secondary considerations. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1354 (Fed. Cir. 2013) (discussing that the burden of production shifts to the patentee “once the court determine[s] that the challenger has established a prima facie case of obviousness”). In other words, the patentee must present evidence to support a finding that a given secondary consideration exists. *See, e.g., Hospira, Inc. v. Amneal Pharm., LLC*, 285 F. Supp. 3d 776, 784 (D. Del. 2018) (citing *Apple Inc. v. Samsung Elec. Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016)); *Prometheus*, 805 F.3d at 1101-02.

96. For objective evidence of secondary considerations to be accorded substantial weight, Plaintiffs must establish a “nexus” between the evidence and the merits of the claimed invention. Courts often exclude evidence of secondary considerations absent a showing of nexus. *See, e.g., Cot’n Wash, Inc. v. Henkel Corp.*, 56 F.Supp.3d 626, 651 (D. Del. 2014) (excluding expert testimony regarding industry praise where no nexus existed), *aff’d sub nom. Cot’n Wash*

Inc. v. Sun Prods. Corp., 606 F. Appx. 1009 (Fed. Cir. 2015); *Inventio AG v. Thyssenkrupp Elevator Corp.*, No. 08-cv-00874-RGA, 2014 WL 5786668, at *8 (D. Del. Nov. 6, 2014) (evidence of secondary considerations properly excluded where plaintiff failed to show nexus to claimed invention), *aff'd*, 622 F. Appx. 906 (Fed. Cir. 2015).

97. Nexus requires a direct connection to the claimed features of the invention as recited in the language of the patent claims. *B.E. Meyers & Co. v. U.S.*, 47 Fed. Cl. 375, 378-79 (Fed. Cl. 2000).

98. Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention.” *In re Kao*, 639 F.3d at 1068 (emphasis in original) (citations omitted); *see also In re GPAC*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) (“For objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.”); *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330 (Fed. Cir. 2017).

99. Even “impressive” evidence of secondary considerations is not “entitled to weight” unless “it is relevant to the claims at issue.” *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994).

100. Even where secondary considerations are established, secondary considerations cannot overcome a strong prima facie showing of obviousness. *See, e.g., Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008); *Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013) (“[W]here a claimed invention represents no more than the predictable use of prior art elements according to established functions,... evidence of secondary indicia are frequently deemed inadequate to establish non-obviousness.”); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (“Given the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate to overcome a

final conclusion that [the claim] would have been obvious.”); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006) (“Secondary considerations of nonobviousness are insufficient as a matter of law to overcome our conclusion that the... claim [at issue] would have been obvious.”); *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997); *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 923 F.Supp.2d 602, 686 (D. Del. 2013) (stating that despite finding the secondary consideration, “[t]he totality of that evidence did not strongly persuade the Court as to [the invention’s] nonobviousness.”).

1. Long-felt need

101. To show the existence of a long-felt but unmet need, the patent owner must show recognition of a problem in the relevant field for a considerable time, that the claimed invention solved the problem, and that the solution was not dependent on unrelated advances in the field. *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332 (Fed. Cir. 2009).

102. In other words, the need must have been a persistent one that was recognized by those of ordinary skill in the art. *In re Gershon*, 372 F.2d 535, 539 (C.C.P.A. 1967) (“Since the alleged problem in this case was first recognized by appellants, and other apparently have not yet become aware of its existence, it goes without saying that there could not possibly be any evidence of either a long felt need in the... art for a solution to a problem of dubious existence or failure of others skilled in the art who unsuccessfully attempted to solve a problem of which they were not aware.”). “The failure of the prior art to mention a problem may be due to the fact that in practice the problem is not a serious one or that a large number of satisfactory solutions is readily apparent.” *Id.*

103. Citation to objective evidence is required. *See In re Kahn*, 441 F.3d 977, 990-91 (Fed. Cir. 2006) (law “requires that the [patentee] submit actual evidence of a long-felt need, as opposed to argument.”). Mere “conclusory” testimony “without evidentiary support” is insufficient. *In re Depomed, Inc.*, 680 F. App’x 947, 953 (Fed. Cir. 2017).

104. A lack of demand because of general satisfaction with the prior art is contrary to a finding of long-felt need. *Nat’l Steel Car. Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1340 (Fed. Cir. 2004) (“Finding of not customer demand is flatly contradictory with [the district court’s] conclusion that a long-felt need existed.”).

105. In order to allege long-felt need, Plaintiffs must “point to [(1)] an articulated and identified problem and [(2)] evidence of efforts to solve the problem that were, before the invention, unsuccessful.” *Apple Inc. v. Samsung Elecs. Co.*, 816 F.3d 788, 804-05 (Fed. Cir. 2016), vacated in part on other grounds on *reh’g en banc*, 839 F.3d 1034 (Fed. Cir. 2016).

106. It is not enough for a patentee to identify drawbacks; the patentee must “show that these drawbacks constituted a long-felt unmet need alleviated by the patent.” *Perfect Web*, 587 F.3d at 1332; *In re Gardner*, 449 F. Appx. 914, 918 (Fed. Cir. 2011).

107. When asserted as a secondary consideration of nonobviousness, analysis of a long-felt but unmet need begins at the time that an identified problem is articulated and ends at the time of filing of the claimed invention. *Tex. Instruments Inc. v. U.S. Int’l Trade Comm’n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993) (“Long-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem.”); *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) (“We look to the filing date of the challenged invention to assess the presence of a long-felt but unmet need.”).

108. “Evidence of the long-felt need factor must squarely address the need satisfied by the asserted claims themselves.” *AstraZeneca LP v. Breath Ltd.*, 88 F. Supp. 3d 326, 387 (D.N.J. 2015), *aff’d*, 603 F. Appx. 999 (Fed. Cir. 2015). The long-felt need must be filled by the patented features, not unclaimed features. *See, e.g., MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1264-65 (Fed. Cir. 2013) (reversing district court on long-felt need for claiming tubing device in fragrance-specific uses because specific claims were not limited to fragrance-specific uses); *Therasense, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1289, 1299 (Fed. Cir. 2010).

109. Even if Plaintiffs provide evidence that the “claimed [invention] may have been beneficial,” that evidence is not probative if “others had previously solved the long-felt need.” *In re PepperBall Techs., Inc.*, 469 F. Appx. 878, 882 (Fed. Cir. 2012); *see also Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988) (“Once another supplied the key element, there was no long-felt need.”).

110. Where the differences between the prior art and the claimed invention are... minimal,... it cannot be said that any long-felt need was unsolved.” *Geo M. Martin Co. v. Alliance Machine Sys. Intern. LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010).

111. “Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness.” *Iron Grip Baseball Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004)) (emphasis added).

2. Surprising or Unexpected Results

112. Whether there are unexpected results is a question of fact. *In re Peterson*, 315 F.3d at 1331.

113. To be considered as evidence of nonobviousness, “unexpected results must be established by factual evidence.” *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). “Mere argument or conclusory statements” by patentee “do[] not suffice.” *Id.*

114. Where differences over the prior art are minor, they cannot lend weight as a secondary consideration. *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (explaining evidence of unexpected properties reflecting a “difference in degree” rather than “difference in kind,” i.e., a new property dissimilar to the known property, cannot overcome obviousness).

115. The relevant time-period for the “unexpected results” inquiry is whether the results would have been unexpected by one of ordinary skill in the art at the time of the patentee’s application and based on knowledge available at that time. *See, e.g., In re Geisler*, 116 F.3d at 1470; *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 460 F. Supp. 2d 659, 667 (D.N.J. 2006) (“Several cases... preclude reliance by an inventor or patentee on undisclosed, later-discovered advantages.”).

116. To support a finding of unexpected results, a patentee must “show that the claimed invention exhibits some superior property or advantage that a [POSA] would have found surprising or unexpected” compared to the closest prior art. *Pfizer*, 480 F.3d at 1370-71; *Geisler*, 116 F.3d at 1469; *Bristol-Myers Squibb Co.*, 752 F.3d at 977 (“To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention.”); *Alcon, Inc. v. Teva Pharm. USA, Inc.*, 664 F. Supp. 2d 443, 464 (D. Del. 2009) (“When ‘unexpected’ and ‘significant’ differences exist between the properties of the claimed invention and those of the prior art, a finding of nonobviousness may be

warranted.”); *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, No. 14-cv-882-LPS, 2017 WL 1199767, at *36 (D. Del. Mar. 31, 2017) (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995)), *aff’d* by 903 F.3d 1310 (Fed. Cir. 2018); *Bristol-Myers Squibb*, 752 F.3d at 977 (“To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention.”).

117. This showing requires “factual evidence,” not merely the unsupported assertions of counsel. *In re Youngblood*, 215 F.3d 1342, at *7 (Fed. Cir. July 6, 1999) (deeming unsupported assertions “insufficient”).

118. Any evidence that is in fact provided should be “weighed against contrary evidence indicating that the results were not unexpected or not a substantial improvement over the prior art.” *See Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 457 (D. Del. 2010), *rev’d on other grounds*, 694 F.3d 1344 (Fed. Cir. 2012).

119. To assert that results were unexpected, “the patent owner must first show ‘what properties were expected.’” *Aventis*, 743 F. Supp. 2d at 348; *see also Pfizer*, 480 F.3d at 1371 (“In order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected.”).

120. Any unexpected property must prove to be a significant benefit in comparison to the prior art. *See Bristol-Myers*, 752 F.3d at 977 (“Unexpected properties, however, do not necessarily guarantee that a new compound is nonobvious. While a ‘marked superiority’ in an unexpected property may be enough in some circumstances to render a compound patentable, a ‘mere difference in degree’ is insufficient.”); *Santarus Inc.*, 720 F.Supp.2d at 457, *rev’d on other grounds*, 694 F.3d 1344 (Fed. Cir. 2012) (explaining that “a party [claiming unexpected results]

must produce evidence demonstrating substantially improved results that are unexpected in light of the prior art”).

121. In order to assert unexpected results, a patentee must present evidence that the results claimed to be unexpected actually occurred. *In re De Blauwe*, 736 F.2d at 705 (“It is well settled that unexpected results must be established by factual evidence.”).

122. Speculation or unproved hypotheses about what might become an unexpected result are simply not enough. *See In re Geisler*, 116 F.3d at 1470.

3. Teaching Away

123. “A reference does not teach away if it does not ‘criticize, discredit, or otherwise discourage’ investigation into the invention claimed.” *Galderma Lab’ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (alteration and citation omitted); *accord, e.g., In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

124. The fact “that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination.” *Syntex (U.S.A) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). “A reference does not teach away, however, if it merely expresses a general preference for an alternative invention.” *Galderma*, 737 F.3d at 738.

125. An entire claim is obvious as long as one embodiment within the claim is obvious. *In re Cuozzo*, 793 F.3d 1268, 1281 (Fed. Cir. 2015).

126. “[T]he teaching away inquiry does not focus on whether a person of ordinary skill in the art would have merely *avored* one disclosed option over another disclosed option.” *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1327 (Fed. Cir. 2017).

127. “When there are only two possible formulations and both are known in the art at the time, the fact that there may be reasons a skilled artisan would prefer one over the other does not amount to a teaching away from the lesser preferred but still workable option.” *Id.*

4. Copying

128. Courts have consistently held that copying has little relevance to obviousness in Hatch-Waxman cases where ANDA filers are required by law to establish bioequivalence to the reference drug product. *See, e.g., Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013); *Purdue Pharma Products L.P. v. Par Pharmaceutical, Inc.*, 642 F.Supp.2d 329, 373–74 (D. Del. 2009) *aff'd at* 377 Fed. Appx. 978, 983 (Fed. Cir. 2010); *Adapt Pharma Ops. Ltd. v. Teva Pharms. USA, Inc.*, 25 4th 1354, 1375 (Fed. Cir. 2022).

C. Person of Ordinary Skill

129. A person of ordinary skill in the art (“POSA”) for the asserted patent claims would have the following qualifications:

A POSA in the subject matter of the patents-in-suit would have been an individual with an advanced degree in pharmacy, chemistry, chemical engineering, or a related field, plus practical experience with pharmaceutical formulations, including their methods of preparation, stability, characterization, and administration, along with a physician or medical professional who administers injectable formulations. For example, (s)he would have had a Ph.D. degree in those areas with about 1-3 years of practical experience or a master's degree with about 5-6 years of such experience.

D. Asserted Claims 1, 7, and 18 of the '802 Patent Are Invalid As Obvious

130. The priority date for the obviousness analysis of claims 1, 7, and 18 of the '802 patent is May 12, 2010.

131. The 2007 Minocin IV label, CN'268, and Gibbs are all prior art because each was published before May 12, 2010.

132. Defendant Nexus has proven by clear and convincing evidence that as of the May 12, 2010 priority date, claims 1, 7, and 18 of the '802 patent would have been obvious to a POSA in view of the 2007 Minocin IV label in combination with CN'268 and Gibbs.

133. A POSA would have been motivated to modify the product described in the 2007 Minocin IV label by adding a magnesium cation and a base to achieve the benefits disclosed in CN'268 and Gibbs, and would have had at least a reasonable expectation of success in doing so.

134. The prior art, including Gibbs, would have motivated a POSA to use molar ratios of magnesium cation to minocycline greater than about 4:1 with a reasonable expectation of success in doing so.

135. A POSA would have been motivated to prepare formulations within the claimed pH range of no less than 4 and no greater than 6, and would have had a reasonable expectation of success in doing so in view of the 2007 Minocin IV label, CN'268, Gibbs, and the knowledge and experience of a POSA.

136. Nexus has established a prima facie case of obviousness with respect to the claimed molar ratio and pH ranges at least because the claimed ranges substantially overlap with the ranges disclosed in the prior art. *See UCB*, 65 F.4th at 687; *In re Peterson*, 315 F.3d at 1329 (citing *Geisler*, 116 F.3d at 1469); *In re Woodruff*, 919 F.2d at 1578; *In re Malagari*, 499 F.2d 1297, 1303 (CCPA 1974)).

137. Regardless of whether the claimed "composition" is construed to refer to a reconstituted intermediate or the diluted composition for administration, a POSA would have reasonably expected to achieve molar ratio and pH values within the claimed range in view of the similarity to the values in the prior art. *See, e.g., In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990) (finding obviousness of "more than 5%" claims where prior art taught "about 1-5%"); *In re Brandt*,

139. The claimed molar ratio and pH ranges are alternatively obvious because they required nothing more than routine optimization. *In re Aller*, 220 F.2d 454, 456 (CCPA 1955) (“it is not inventive to discover the optimum or workable ranges by routine experimentation”).

141. Even if not inherent, the injection site hemolysis limitation of claim 1 of the '802 patent would have been obvious as expected to a POSA and taught in view of the 2007 Minocin IV label in combination with CN'268 and Gibbs.

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149. Plaintiffs have failed to meet their burden to show any surprising or unexpected results sufficient to weigh against the strong obviousness of claims 1, 7, and 18 of the '802 patent.

150. Plaintiffs have failed to meet their burden to show any teaching away sufficient to weigh against the strong obviousness of claims 1, 7, and 18 of the '802 patent.

151. Plaintiffs have failed to meet their burden to show copying sufficient to weigh against the strong obviousness of claims 1, 7, and 18 of the '802 patent.

152. Claims 1, 7, and 18 of the '802 patent are invalid as obvious under 35 U.S.C. § 103.

E. Asserted Claim 27 of the '105 Patent Is Invalid As Obvious

153. The priority date for the obviousness analysis of claim 27 of the '105 patent is May 12, 2010.

154. The 2007 Minocin IV label, CN'268, and Gibbs are all prior art because each was published before May 12, 2010.

155. Defendant Nexus has proven by clear and convincing evidence that as of the May 12, 2010 priority date, claim 27 of the '105 patent would have been obvious to a POSA in view of the 2007 Minocin IV label in combination with CN'268 and Gibbs.

156. A POSA would have been motivated to modify the product described in the 2007 Minocin IV label by adding a magnesium cation to achieve the benefits disclosed in CN'268 and Gibbs, and would have had at least a reasonable expectation of success in doing so.

157. The prior art, including Gibbs, would have motivated a POSA to use molar ratios of magnesium cation to minocycline greater than about 3:1 with a reasonable expectation of success in doing so.

158. A POSA would have been motivated to prepare an intravenous minocycline formulation that does not comprise a pharmaceutically acceptable oil and would have had a

reasonable expectation of success in doing so in view of the 2007 Minocin IV label, CN'268, Gibbs, and the knowledge and experience of a POSA.

159. A POSA would have been motivated to prepare formulations within the claimed pH range greater than 4 and less than 7 and would have had a reasonable expectation of success in doing so in view of the 2007 Minocin IV label, CN'268, Gibbs, and the knowledge and experience of a POSA.

160. Nexus has established a prima facie case of obviousness with respect to the claimed molar ratio and pH ranges at least because the claimed ranges substantially overlap with the ranges disclosed in the prior art. *See UCB*, 65 F.4th at 687; *In re Peterson*, 315 F.3d at 1329 (citing *Geisler*, 116 F.3d at 1469); *In re Woodruff*, 919 F.2d at 1578; *In re Malagari*, 499 F.2d at 1303.

161. Regardless of whether the claimed “composition” is construed to refer to a reconstituted intermediate or the diluted composition for administration, a POSA would have reasonably expected to achieve molar ratio and pH values within the claimed range in view of the similarity to the values in the prior art. *See, e.g., In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990) (finding obviousness of “more than 5%” claims where prior art taught “about 1-5%”); *In re Brandt*, 886 F.3d 1171, 1177 (Fed. Cir. 2018) (prima facie case of obviousness for “less than 6 pounds per cubic feet” claims where prior art taught “difference between abutting ranges was “virtually negligible”).

162. Dr. Friedman’s allegation that Lactated Ringer’s was not the “standard of care” does not overcome obviousness at least because he admitted that “it is known [from the prior art label] that you could use Lactated Ringer’s to dilute the formulation” and the administration pH for that “standard option available to the person of ordinary skill in the art was 4.5 to 6.0.” Tr.

727:14-19, 728:3-6. *See, e.g., Bayer Pharma*, 874 F.3d at 1329 (obviousness does not require “the preferred, or most desirable” options) (internal citations and quotations omitted).

168. Plaintiffs have not presented evidence sufficient to demonstrate any secondary consideration or objective indicia sufficient to weigh against the obviousness of claim 27 of the '105 patent.

169. Plaintiffs have failed to demonstrate the asserted claims are reasonably commensurate in scope with the current commercial Minocin IV product and thus have failed to demonstrate nexus to any alleged secondary consideration or objective indicia. *See In re Kao*, 639 F.3d at 1068.

170. Plaintiffs have failed to meet their burden to show any long-felt need sufficient to weigh against the strong obviousness of claim 27 of the '105 patent.

171. Plaintiffs have failed to meet their burden to show the mere passage of time related to FDA approval of the old Minocin IV product is relevant to or weighs against the strong obviousness of claim 27 of the '105 patent.

172. Plaintiffs have failed to meet their burden to show any surprising or unexpected results sufficient to weigh against the strong obviousness of claim 27 of the '105 patent.

173. Plaintiffs have failed to meet their burden to show any teaching away sufficient to weigh against the strong obviousness of claim 27 of the '105 patent.

174. Plaintiffs have failed to meet their burden to show copying sufficient to weigh against the strong obviousness of claim 27 of the '105 patent.

175. Claim 27 of the '105 patent is invalid as obvious under 35 U.S.C. § 103.

IV. 35 U.S.C. § 112

A. Legal Standards

1. Indefiniteness

176. A patentee must particularly point out and distinctly claim the subject matter that she regards as her invention. 35 U.S.C. § 112 ¶ 2. “[A] patent is invalid for indefiniteness if

its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

177. The Supreme Court has explained that there are several components to determining definiteness, including: (1) evaluating from the perspective of a POSA; (2) reading claims in light of the patent’s specification and prosecution history; and (3) assessing the claims from the perspective of a POSA “*at the time the patent was filed.*” *Id.* (emphasis in original).

178. The claim itself and the patent’s specification are the primary sources for purposes of indefiniteness analysis. *IBSA Institut Biochimique, S.A. v. Teva Pharms. USA, Inc.*, 966 F.3d 1374, 1380-81 (Fed. Cir. 2020) (assessing extrinsic record only after establishing claim’s boundaries remain unclear from claim and specification).

179. “‘Even if a claim term’s definition can be reduced to words, the claim is still indefinite if a person of ordinary skill in the art cannot translate the definition into meaningfully precise claim scope.’” *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1251 (Fed. Cir. 2008). Written Description

180. A patent cannot claim more than it describes. *See* 35 U.S.C. § 112, ¶ 1 (2012) (“The specification shall contain a written description of the invention...”); *Ariad Pharm. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (“The description must clearly allow [POSAs] to recognize that [the inventor] invented what is claimed.”) (citation and internal quotation marks omitted).

181. “The test for [written description] sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date... Possession as shown in the

disclosure is a more complete formulation.” *Ariad*, 598 F.3d at 1351 (internal citations omitted). To fulfill the written description requirement, the patent owner must indicate his or her possession of the invention at the time of filing the patent application as indicated by “an objective inquiry into the four corners of the specification.” *Id.* This inquiry presents a question of fact. *Id.*

182. Further, “[t]he description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention.” *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). “To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that ‘the inventor invented the claimed invention.’” *Id.* at 1566 (quoting *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997)).

183. A specification provides adequate written description if it reasonably conveys to a POSA that the inventor had possession of the **entire** claimed subject matter as of the filing date. *See Ariad, Inc.*, 598 F.3d at 1351-52; *Boston Sci. Corp. v. Johnson & Johnson Inc.*, 647 F.3d 1353, 1366 (Fed. Cir. 2011). Ultimately, “it is in the patent specification where the written description requirement must be met.” *Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 927 (Fed. Cir. 2004).

184. “The purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not over-reach the scope of the inventor’s contribution to the field of art as described in the patent specification”) (internal quotations omitted). *Ariad*, 598 F.3d at 1353-54.

185. The written description is not a question of whether a POSA might be able to construct the patentee’s invention from the teachings of the disclosure. Rather, it is a question of

whether the application “necessarily discloses” the particular invention. *See Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1327 (Fed. Cir. 2000) (quoting *Martin v. Mayer*, 823 F.2d 500, 505 (Fed. Cir. 1987)). “A description that merely renders the invention obvious does not satisfy the requirement.” *Ariad*, 598 F.3d at 1352.

186. The specification itself must demonstrate that the inventor was in possession of the *entirety* of the claimed invention. *See Ariad*, 598 F.3d at 1352.

2. Enablement

187. Enablement is a question of law based on underlying factual inquiries. *See ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010). A patent specification must provide sufficient information to allow a POSA to make and use the invention claimed. *See* 35 U.S.C. § 112, ¶ 1. A specification lacks enablement if it fails to teach a POSA “how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (citing *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)).

188. The enablement “doctrine prevents both inadequate disclosure of an invention and overbroad claiming that might otherwise attempt to cover more than was actually invented. Thus, a patentee chooses broad claim language at the peril of losing any claim that cannot be enable across its full scope of coverage.” *See, e.g., MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012); *see also Janssen Pharm. N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317 (Fed. Cir. 2009) (invalidating method patent for treatment of Alzheimer’s with galanthamine invalid for lack of enablement).

189. “Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (listing optional factors); *see also Amgen, Inc. v. Sanofi*,

191. Even where a patent specification “recognizes a specific need” and “suggests a theoretical answer to that need,” just providing “a starting point from which one of skill in the art can perform further research in order to practice the claimed invention [] is not adequate to constitute enablement.” *Nat’l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1198 (Fed. Cir. 1999).

192. A POSA cannot determine with reasonable certainty the scope of the invention, because injection site hemolysis is not defined and it is not understood how to measure if there has been a reduction. *See Nautilus*, 572 U.S. at 909-10.

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194. Claims 1, 7, and 18 of the '802 patent are invalid because the claimed reduction in injection site hemolysis is an indefinite term and the patent does not provide a POSA with the requisite clarity to know the scope of the claimed invention.

C. Injection Site Hemolysis Lacks Written Description and Lacks Enablement

195. A POSA would not have known how to measure injection site hemolysis, and thus could not practice the full scope of claim 1 of the '802 patent. *See Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013).

196. Similar to *Trustees of Boston Univ.*, the '802 patent claims' breadth is not justified by the limited disclosure of hemolysis measurements in highly artificial setting, because the asserted claims all require administering the claimed formulation to a subject. *Trustees of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1363-65 (Fed. Cir. 2018).

197. Importantly, the Federal Circuit has construed the full scope of a patent claim to cover the entire scope, not a majority of the scope of a claim. *Id.* (holding enablement of five out of six permutations of the claimed invention is not full scope enablement).

198. The patent also cannot claim more than what was described and a POSA would understand the inventors possessed as of the priority date. 35 U.S.C. § 112; *Ariad Pharm.*, 598 F.3d at 1351.

199. Claims 1, 7, and 18 of the '802 patent all require a reduction in injection site hemolysis with the claimed minocycline formulation, however, the patent fails to adequately inform a POSA how to practice this claim limitation, because there is no method for measuring injection site hemolysis.

200. Claims 1, 7, and 18 of the '802 patent also fail to inform a POSA that the inventors possessed the invention as of May 12, 2010.

D. Claims 1 and 18 of the '802 Patent and Claim 27 of the '105 Patent Lack Written Description and Enablement for the pH Limitations

201. A patent's specification "must enable [a POSA] to practice the full scope of the claimed invention," however the specifications of the patents-in-suit fail to enable across the full scope of claimed pHs. *See AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1243-45 (Fed. Cir. 2003).

202. As described above, Table 30 of the patent specification shows that at certain pH's and concentrations, the claimed formulation is insoluble, and thus cannot be administered to a subject. Therefore, "the specification clearly and strongly warns that such an embodiment" would not work, even though it is within the scope of the claims. *AK Steel*, 344 F.3d at 1244.

203. It is well-accepted that the enablement doctrine prevents both insufficient disclosure and overbroad claiming. "Thus, a patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope of coverage." *MagSil*, 687 F.3d at 1381. Here, Plaintiffs claimed broad embodiments of minocycline formulations for intravenous administration, however, they have done so at their own peril, because the specification itself shows not all of those embodiments are enabled.

204. Similarly, Plaintiffs did not describe a sufficient breadth of embodiments to show possession of the full scope of the pH limitations, but the opposite. The specification shows that Plaintiffs did not possess the full scope of the asserted claims at pH 6. The specification must demonstrate that the inventor was in possession of the entirety of the claimed invention. *Ariad*, 598 F.3d at 1352.

205. Plaintiffs allege that the molar ratios of magnesium to minocycline enabling a POSA to intravenously administer minocycline is a novel aspect of their asserted claims, but the specification does not supply that information, but rather only supplies the conclusion that

CERTIFICATE OF SERVICE

The undersigned certifies that on July 26, 2023, the foregoing document was served on counsel of record by operation of the Court's CM/ECF system.

/s/ Matthew Wilkerson